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Dr. William George MacCallum
1874–1944

Dr. William George MacCallum[1]

1874–1944

Dr. William George MacCallum was born in Dunnville, Ontario, on the 18th of April, 1874. He was the second of four children, having an elder and a younger sister, and a younger brother, John Bruce MacCallum, whose brilliant career in medical research was cut short by his death from tuberculosis at the age of thirty.[2] His mother, Florence Octavia Eakins, was born in Sparta, Ontario. She was an accomplished pianist and singer, and from her, doubtless, Dr. MacCallum acquired his deep and life-long love of music. His father, George Alexander MacCallum, born in Stouffville, Ontario, was a general practitioner with an active practice in the countryside surrounding Dunnville. Later, he served as medical superintendent of two hospitals for the insane in Ontario. As a youth, Dr. MacCallum often rode with his father on visits to patients, and helped him at times during operations by administering ether, and by "purifying the air of the room" with the Lister carbolic spray.

The elder MacCallum had a consuming interest in natural history. He was an insatiable collector, and the home became filled with stuffed wildcats, foxes, snakes, birds and other animals; with birds' eggs; and with Indian relics. This remarkable collection was later given to Queen's University. When the family moved to New York after Dr. MacCallum had become professor of pathology at Columbia University, his father, then about seventy years of age, became pathologist of the Bronx Zoo and of the Aquarium, and, at the suggestion of the younger MacCallum, he entered upon a study of the worm parasites of captive animals—a subject which he pursued eagerly for many years thereafter, and to which he made numerous contributions. He died in 1936 at the age of 93.

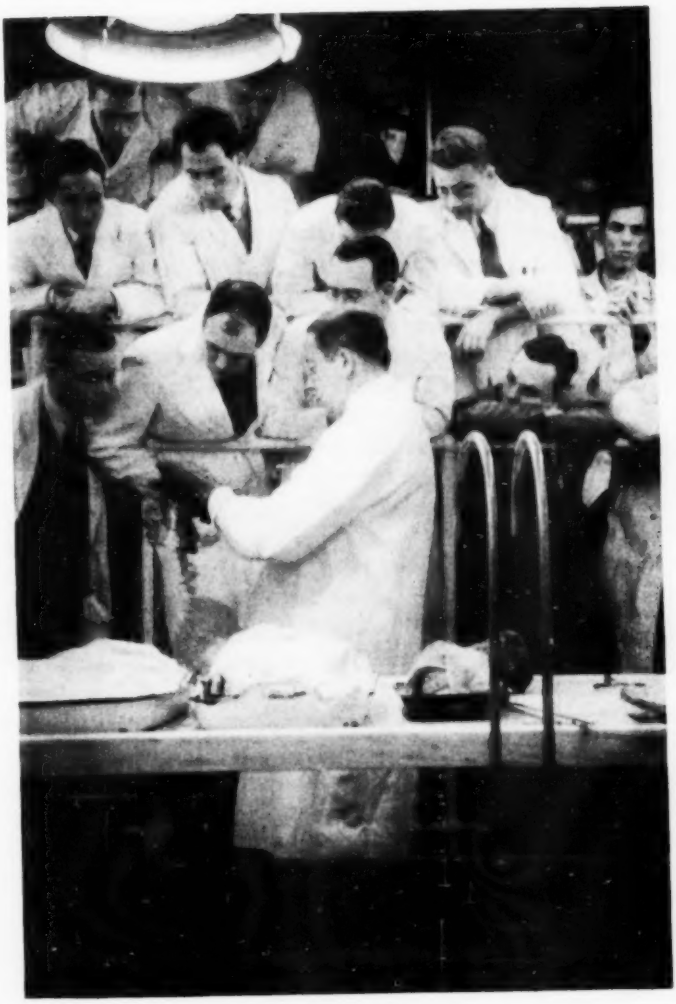
Dr. MacCallum was taught at home until he was nine years of age. He then attended public school, and at the early age of fifteen passed

[1] Reprinted, with some additions, from a sketch written for the *Archives of Pathology*.

[2] A biography of this brother, by Archibald Malloch, has been published under the title "Short Years."

the entrance examinations at the University of Toronto with First Class Honours. He entered the University at sixteen years of age, completing in four years the requirements for the B.A. degree and, in addition, a sufficient number of medical courses to enable him to enter the second year class of the Johns Hopkins Medical School, in the company of the small group who, in the preceding year, had been the first students to be admitted to the newly opened school. At the suggestion of Dr. A. E. Malloch, a friend of Dr. Osler and of the MacCallums, he wrote to Osler asking if he could be admitted to the second year class. Osler replied that admission with advanced standing could not be permitted, as no such precedent existed in the school. Since the school itself had not been in existence long enough to have had a precedent of that sort, young MacCallum ventured to direct further correspondence to Dr. Welch, who was then Dean, and was accepted. In 1897, at the age of twenty-three, he was graduated at the head of his class. After a year spent in a rotating interneship in the Johns Hopkins Hospital, he applied, without success, for a place on Osler's staff. Dr. Welch then offered him an assistantship in pathology, which he accepted. He progressed rapidly in rank, becoming associate professor of pathology in 1902. In 1905, he and Dr. Harvey Cushing planned and supervised the building of the Hunterian Laboratory, and he then initiated a pioneering course in pathological physiology. In 1908 he was made professor of pathological physiology and lecturer in forensic medicine. The following year he succeeded Dr. Prudden as professor of pathology at Columbia University, where he remained until 1917, when he returned to Johns Hopkins to succeed Dr. Welch as Baxley Professor of Pathology.

Dr. MacCallum's interest in scientific investigation early manifested itself. While an undergraduate student at the University of Toronto he was awarded a gold medal for a paper on worm parasites; and it is significant that one of his most important contributions was made at home during the summer vacation following his graduation from medical school. This was the discovery that the flagellated form of the malarial parasite represents the sperm cell, a fact which provided the key to the solution of the life-cycle of the parasite. Young MacCallum reported his discovery at a medical meeting in Toronto, at which Lord Lister presided. Some years later Sir Ronald Ross said



DR. MACCALLUM TEACHING

about this discovery by the young medical student: "I have ever since felt disgraced as a man of science!"; for Ross had erroneously interpreted the sperm cell wriggling into the penetrated female cell as being a flagellated spore trying to escape from it.

His next contribution of major importance was published several years later, when he was twenty-eight years of age. This was the demonstration that the lymphatic vessels constitute a closed system with continuous walls, instead of having openings in communication with the tissue spaces, as was widely believed at that time. The far-reaching significance of this fact in relation to the physiology and pathology of the tissue fluids and the lymph, needs no comment. This paper was followed by one in which he clearly demonstrated for the first time the mechanism of absorption of granular materials and red blood cells from the peritoneal cavity.

In 1905, at the age of thirty-one, Dr. MacCallum published the first of the series of his studies which revealed the function of the parathyroid glands. By means of beautifully contrived experiments he and Voegtlin showed that the calcium in the blood is maintained at a normal level by the activity of these minute glands; that an insufficient parathyroid secretion leads to a loss of calcium from the blood; that the normal amount of circulating calcium is necessary to temper the excitability of the motor nerves; that the fatal tetany which results from insufficient parathyroid secretion is due to the diminished calcium content of the blood; and, finally, that the symptoms of tetany can be made to disappear at once by the administration of calcium. This investigation represents one of the most important of the pioneering studies on the functions of the glands of internal secretion.

Another fundamental study, published in 1909 at the age of thirty-five, established the fact that the function of the pancreas in relation to carbohydrate metabolism and diabetes is localized in the islands of Langerhans. This had been suspected from the morphological observations of Opie and others, but had remained unproved and uncertain until Dr. MacCallum showed that when the pancreatic duct is ligated, all of the pancreatic glandular tissue except the islands undergoes atrophy and disappears, but diabetes does not occur. If, however, the remaining film of tissue containing only the islands be extirpated, diabetes follows immediately. The procedure (duct ligation) employed by Dr. MacCallum in order to destroy the acinar

tissue while leaving the islands intact was later adopted by Banting and Best in their successful attempt to extract from the islands the anti-diabetic hormone (insulin) which Dr. MacCallum's experiments had shown to be secreted by those cells.

Other contributions to pathological anatomy and physiology, which cannot be outlined here, are contained in his bibliography of one hundred and seventy-three papers, which include biographical sketches and studies in medical history, a subject in which he had an enduring interest. In his superb biography of Dr. W. S. Halsted one can read between the lines much of his own attitude toward science, toward life and toward his fellow-man.

No discussion of his contributions could stop short of the mention of that work which has had so wide an influence throughout the English-speaking world, namely, his "Text-Book of Pathology". This book, which appeared in 1916, was written in a lucid and engaging style, and with an inquiring, critical attitude made sound by a rich personal experience with the subject matter. It was a landmark in the history of text-books of pathology, for it represented the first attempt to treat the entire subject from the standpoint of etiology. In this book the attempt was made to present the effects that each form of injury, each cause of disease, produce in the whole body, instead of following the traditional method of cataloguing all of the heterogeneous and unrelated injuries that can affect each separate organ. Of course, because of the incomplete state of knowledge, it was impossible to write of all morbid conditions from a strictly etiological standpoint, and compromises had necessarily to be made; but Dr. MacCallum's attempt has been widely regarded as a fundamentally important move in the right direction. The extraordinary success of the book in this country and abroad in the past twenty-eight years during which it has passed through seven editions, attests plainly enough the approval which his method of treatment of the subject aroused.

While at Columbia he played an important rôle in the progressive reform that abolished the political coroner system in New York City, and introduced the much superior system through which the examiner of medico-legal cases must be a skilled pathologist, selected from the civil service list by competitive examination; and in Baltimore he was associated with a similar reform.

In recognition of his scientific attainments he was made a member of

the National Academy of Sciences in 1921. He was also an Honorary Fellow of the Royal Society of Medicine, London, 1918; Honorary member, Pathological Society of Great Britain and Ireland, 1940; Honorary Member, Societas Medicorum Sverana, Stockholm, 1918; Corresponding Member, Societas Regia Medicorum, Budapest, 1938; Honorary Member, Societé d'Endocrinologie, Paris, 1939; Hon. D. Sc., University of Toronto, 1927. He was a member of numerous American medical societies but, save for the Association of American Physicians, he rarely attended society meetings.

The last entry in a year-to-year outline of his activities that he kept reads: "1941. War advanced throughout Europe. Have been in Marburg for several days, confusion of pronunciation, etc., also in country for days. Going to Winter Park, Florida." At Winter Park he suffered a stroke that paralyzed the right side, and robbed him of speech. He remained bed-ridden thereafter until his death on the third of February, 1944.

Dr. MacCallum's nature was of a complexity that renders it impossible to sketch his personality satisfactorily in a few simple strokes. He was a man of strong likes and dislikes, and contradictory emotional forces were not infrequently at play. He lived simply, though he was very responsive to beautiful and tasteful surroundings, and had a gourmet's appreciation of the pleasures of the table. He had wide cultural interests. He greatly enjoyed good conversation on all manner of subjects save politics and metaphysics, and was a delightful, sparkling and stimulating conversationalist. Though he would converse eagerly for hours with those who could ably cross swords with his keen mind, he would become quickly and profoundly bored with dull or pompous persons, and his boredom on such occasions could be appallingly evident. He had a fine sense of humor which, when properly stirred, would cause him to laugh until tears came. In conversation he was always at his best with a single companion or with one or two intimates, for, in spite of his acquired ease among people, he was basically a shy and sensitive person. His fastidiousness in personal contacts, and his aloofness that bordered at times upon the brusque, were attributable in part to his inherent shyness. "I was never a good mixer", he once said. "I scarcely got to know my classmates at Toronto." He shrank from the familiarity that most men find agreeable, and would actually wince on the rare occasions when

some venturesome colleague would call him Bill. It is therefore somewhat anomalous that, through his association with J. L. Nichols, he became one of the founders of the Society of Pithotomists, a medical students' club that is still in active existence. In 1896, in his last year as a medical student, he and Nichols, a classmate, rented a house at 1200 Guilford Avenue. As a housewarming they invited Dr. Welch, Dr. Osler and others of the faculty, and a few friends, and entertained them with a small keg of beer. Everyone had such a good time that the performance was repeated; and shortly thereafter seven classmates joined with MacCallum and Nichols to perpetuate the idea, some of them taking rooms in the house. A club was thus formed, and MacCallum manufactured from the Greek the term "pithotomy" for the periodic operation of opening the keg. He maintained a rather wistful interest in the activities of the club throughout his life, but it was always a distant interest, and he was never seen at the later annual "pithotomies", which eventually became quite elaborate, and which have long been attended by the students and by most of the other members of the medical school faculty.

He remained a bachelor, but he thoroughly appreciated the society of attractive and intelligent women, not a few of whom remained his devoted admirers throughout the years, being drawn to him by his personal charm, his courtly, thoughtful ways, his splendid and artistically sensitive mind and, possibly, in the instances in which their attitude was a motherly one, by their intuitive recognition of his ordinarily concealed shyness. He had a charming and disarming way with children, that immediately won their confidence. He himself possessed a marked degree of filial piety, and his concern over his ageing parents was deep, unremitting and touching.

Though possessing an excellent physique, he cared nothing for sports, whether as a participant or as a spectator. He was very fond of travel, and his trips to far away lands were usually enlivened by the performance of autopsies on cases with extreme lesions or with diseases unfamiliar in this clime, and by the search for new parasites in tropical animals. He would return laden with notes and interesting pathological material. On his last visit to the Orient he wrote from Singapore in a discouraged vein: "There are none of the wonderful things I used to see. The commercial exploitation of 606 or something like it has ruined the syphilis. There is no malaria. I've done cases of tu-

berculosis of the lungs, epithelioma of the oesophagus, etc., etc., and I doubt whether I'll have anything worth bringing home. I'm afraid it will be just the same in Rangoon. There are no worm parasites any more either. I've found one hookworm, and before everybody had all these things. But what is the good in coming out here to do autopsies on cases of carcinoma of the stomach and tuberculous peritonitis!" But soon he would be describing vividly the strange landscapes, golden pagodas, and women in bright dresses smoking cheroots of huge size. He took many photographs of the scenes of his travels, and these he would have made into lantern slides on his return to exhibit to small groups of friends, with delightful running comments.

His absorbing interest in pathology was carried into all sorts of situations. He was continually on the alert for evidences of disease in people upon the streets or in public conveyances. Sometimes he would place a section under his microscope, ask for a diagnosis, and after a discussion of the lesion he would smilingly say: "I saw a curious speck in a filet mignon last week at the Blank's dinner party, and I cut it out and slipped it into my pocket and had a section made." Hostesses who learned of this penchant have confessed to a degree of nervousness during the main dinner course when he was a guest.

He loved science, and his scientific ideals were of the purest. He hated dogmatism and cant in whatever relation, and was, himself, completely free from those blights of the spirit. He was a teacher of great simplicity and charm, and he deeply enjoyed his contacts with the medical students. His relations with most of the members of his staff were not very close. It was as though he hesitated to intrude himself into their activities, for he always seemed pleased when they came into his laboratory to consult him. In their turn, they felt hesitant about intruding upon him. They were given the broadest freedom of action, but this freedom was tempered by the unpremeditated, constant example of his own high scientific ideals, his continually enquiring attitude, his freedom from dogmatism, and his devotion to the accurate and meticulous study of the manifestations of disease. The influence of his attitude, which pervaded the department, had an enduring effect upon most of those who became members of his staff, and few have worked in his department who have not acquired, from his example, a deeper appreciation of the pleasures and satisfactions of a free spirit of enquiry, disciplined by a high regard for accuracy of thought and observation.

ARNOLD R. RICH.

DISSECTING ANEURYSM PRODUCING CORONARY OCCLUSION BY DISSECTION OF THE CORONARY ARTERY

CHARLES W. WAINWRIGHT, M.D.

From the Department of Medicine,
Johns Hopkins University School of Medicine

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In 1912 (1) Herrick drew attention to the fact that acute coronary thrombosis was, indeed, a frequent occurrence and a much overlooked and poorly understood condition. Following this classic paper the diagnosis was made with increasing frequency until now the wards of any large hospital are scarcely ever without one or more cases so diagnosed. Diagnostic skill has developed to such a degree that the recognition of this condition has become commonplace. So enthusiastic have doctors become for the diagnosis that twenty-five years later Herrick (2) felt it necessary to remind us that whereas formerly acute coronary thrombosis had been called something else, we were now falling into the error of making the diagnosis too freely; failing frequently to apply the critical study which in so many instances would avoid the error. Many conditions may lead us to this error. Pulmonary embolism, acute pericarditis and dissecting aneurysm are the conditions most often mistaken for it. At times there may be no difficulty whatever in differentiating these from acute coronary thrombosis. They are readily recognized when the signs and symptoms presented are classical and the circumstances which have led up to the incident leave little doubt that the event was other than an acute coronary occlusion. However, it may be exceedingly difficult, if not impossible, to differentiate these three conditions until subsequent events make clear what has happened. When pulmonary embolism is accompanied by cardiac signs and symptoms and the electrocardiogram is similar to that of posterior myocardial infarction, it is easily confused with acute coronary occlusion. When the source of the infection is obscure, and the electrocardiogram closely simulates that of myocardial infarction, acute pericarditis may lead to great difficulty. Dissecting aneurysm, when accompanied by shock and presenting electrocardiographic changes,

as it frequently does, and later fever and leucocytosis, may defy the greatest diagnostic skill and be impossible of correct interpretation. This problem presents itself not so infrequently and is a differentiation which one must make, indeed, often.

As taxing as it may be upon one's diagnostic ability to interpret properly signs and symptoms such as those of dissecting aneurysm or acute coronary occlusion, it is even more difficult to recognize these two conditions when they exist concomitantly. When one reflects upon it, it is remarkable that they do not often coexist. It is singular that it is not more regularly found at autopsy that the dissection of an aneurysm has extended along one or both of the coronary arteries. Dissection along peripheral arteries occurs with great frequency. When one recalls that the initial rupture of the intima of the aorta almost always takes place about four to five centimeters above the base of the aorta, it seems reasonable to anticipate that dissection of the coronary arteries would occur often. It is, however, an uncommon occurrence. A careful search of the autopsy records of the Johns Hopkins Hospital failed to disclose a single instance until 1942. A review of the literature fails to reveal a report of such an occurrence with the exception of one case reported by Weiss (3) in 1938. In 1935 Lawrence (4) reported a case of dissecting aneurysm in which there was some narrowing of the coronary orifices but the vessels were patent. Again in 1935, Reisinger (5) reported a case in which there was a small ecchymosis beneath the anterior coronary artery but the source of the blood was not clear. Recently Bayley and Monte (6) have reported an instance of dissecting aneurysm in a man fifty-two years of age with hypertension in which the dissection produced an insufficiency of the aortic valve. Electrocardiographic changes were present which to them suggested impairment of blood flow through the right coronary artery. The patient died as a result of rupture of the aneurysm into the pericardial sac. A clot in the aortic wall partially surrounded the intramural portion of the right coronary artery. No actual change had occurred in the heart muscle and the authors interpreted the electrocardiographic changes as due to an area of acute myocardial ischemia produced by this partial compression of the right coronary artery.

The case of Weiss (3) was that of a forty-year-old Filipino who was

seen a year before his death. At that time his blood pressure was 178/120 and he was bleeding from a peptic ulcer. A year later he developed sudden, boring, nonradiating pain in the epigastrium and when seen was in shock, the blood pressure being 100/55. The white blood cell count was 27,600. An electrocardiogram taken at that time showed T_1 and T_2 diphasic, T_3 upright and T_4 inverted. There was slight left axis deviation. These changes were interpreted as indicating myocardial infarction. The following day T_1 and T_2 were diphasic and T_3 inverted, and the Q-T segment of Lead III was prolonged. It was thought that these alterations as compared with those of the previous day indicated progressing myocardial change. At autopsy, a dissecting aneurysm was found, the lateral aspect of the left ventricle was lighter than normal and contained yellowish and reddish areas. About the mouths of both coronary arteries, there was a marked degree of extravasation of blood. The left coronary was compressed near its opening by a dissection which extended for a distance of about 1 centimeter from the orifice along the course of the artery. The vessel contained no thrombus.

Why does not coronary dissection occur more often with dissecting aneurysm? The proximity of the coronary orifices to the reflection of the pericardium on the aorta may prevent dissection from proceeding very far before a rupture into the pericardium takes place. It may be that the anatomical relations of the orifices in the sinus of Valsalva afford protection against such an occurrence. In any event, the infrequency with which it has been recognized would seem to indicate that it is a rare occurrence but it is quite possible that it has escaped notice.

An instance of coronary dissection resulting in occlusion of the vessel has come to our attention in the wards of the Johns Hopkins Hospital and forms the basis for this report. The diagnosis of dissecting aneurysm was made before death although the evidence strongly suggested that a coronary occlusion had occurred.

CASE REPORT

History: #258231. M.C., a colored maid, 42 years of age, entered the hospital on April 19, 1942, complaining of pain in the chest. She always had been healthy. Five or six months prior to admission, she had begun to experience fatigue and nervousness and occasionally had

dizzy spells. Three weeks before admission, she had a small nosebleed and noticed a little shortness of breath on exertion. There had been family difficulties and she was very nervous and emotionally upset.

On the evening of April 19th, while lifting a stack of plates to a shelf above her head, she was suddenly seized with excruciating pain, which began in the epigastrium and radiated up over the chest to the right arm and back. She gasped for breath, began to wheeze loudly and broke into a profuse sweat. The pain was so intense that she sank to the floor on her hands and knees. The pain was not relieved by medicine given her but continued as a sharp, knifelike pain, of greatest intensity over the right side of the chest and under the right shoulder blade. Obtaining no relief, two hours after the onset of the pain, she was brought to the accident room of the hospital where she was given morphine hypodermically and was then sent to the ward.

Physical Examination: T. 101°, P. 120, R. 28, B.P. 220/135. The patient was a rather obese woman, obviously very ill, and in severe pain, despite the morphine that had been given her. She was sweating profusely and gasping for breath. The eyes were normally prominent, the pupils were equal and reacted actively to light. The retinal arteries showed a considerable degree of arteriosclerosis and two small hemorrhages were seen in the right eye. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The lungs were apparently clear but examination was difficult because of the patient's precarious condition. The heart was somewhat enlarged to the left and the dullness over the manubrium seemed to be widened. All over the heart a systolic murmur was heard which was loudest in the fourth intercostal space to the left of the sternum. The sounds were forceful and clear and the second aortic sound was greatly accentuated. A gallop rhythm was present and occasional ventricular extrasystoles occurred. Above the right clavicle a pulsating mass was seen which was thought to be a dilatation of the common carotid artery. Pulsations were prominent in the arteries of the extremities but they were not noticeably thickened. The radial pulses were equal. There was no abdominal tenderness, no masses were felt, and the liver and spleen were not enlarged. The neurological examination was negative except for hypoactive reflexes.

Course in the Hospital: The patient lived for eighteen days after

being admitted to the hospital. The day following admission her temperature reached 102°. It gradually fell and seven days later had reached normal where it remained for eight days. Then it again began to rise and thereafter varied between 99° and 100.6°. The pulse was always rapid, at first varying from 100 to 130, later from 90 to 100 and during the last few days of life from 100 to 148. For several days after admission, she complained of pain in the chest which was relieved by nitroglycerine. The pulse in the peripheral arteries was carefully observed and no change was noted except that the pulsations were always prominent. After a few days, the chest pain disappeared and the patient seemed much improved. The blood pressure remained at a high level, the systolic pressure varying between 210 and 230 and the diastolic pressure between 110 and 160.

On the tenth hospital day, the patient began to menstruate at a time when the period was not expected. This was accompanied by severe abdominal pain, with tenderness and muscle spasm in the left lower quadrant of the abdomen. A pelvic examination revealed the presence of masses in both fornices suggesting chronic salpingitis. At this time a few red blood cells appeared in the urine. Her symptoms gradually subsided and again she seemed better.

On the fifteenth day in the hospital, her temperature began to rise, the pulse and repiratory rate increased, there was profuse sweating, and cyanosis developed. The blood pressure dropped to 150/60. Numerous rales were heard at the bases of both lungs and for the first time a blowing diastolic murmur was heard to the left of the sternum. The white blood cell count which previously had varied from 17,000 to 20,000, now rose to 24,000. The patient complained of increasing pain in the chest and upper abdomen, of greatest intensity in the right side of the chest and below the angle of the right scapula. From time to time she vomited. The rales in the lungs increased and the liver became palpable. On the eighteenth hospital day, the blood pressure was 120/70. The patient was at this time in a critical state, the extremities cold, the heart's action irregular, and in this condition she died on May 7, 1942.

Laboratory Data: Blood (on admission): Hb. 12.49 gms.; RBC: 5,500,000; WBC: 22,800. Sedimentation rate (on admission): 5 mm. in 1 hr. 5th day: 25 mm.; subsequently it fell to 12 mm. in 1 hr.

Serological test for syphilis: negative. Urine: sp. gr.: 1.010 to 1.020. On admission, no albumin; later, a trace; finally, 1 plus. Shortly before death a few red blood cells and a few leucocytes were present in the sediment. Urine culture: sterile. Roentgenograms: 4 days after admission: *Chest:* cardiac outline enlarged; diffuse widening of aortic shadow. 8 days after admission: aorta still quite large; some of the apparent enlargement due to distortion incident to portable examination.

Electrocardiograms: Day after admission: Normal sinus rhythm. P-R interval: .16 sec. Left axis deviation. T_1 shallowly inverted. T_2 iso-electric. T_{4F} inverted with coved S-T segment. 7 days after admission: T_1 and T_{4F} have become deeply inverted, classical "coronary T-wave" pattern. T_2 is also shallowly inverted; T_3 higher. This sequence of changes is diagnostic of recent anterior myocardial infarction. 15th day after admission: There is a striking change in the configuration of all of the complexes. The S-T segment in Leads I, II and 4F are depressed. The T waves are now all upright. The record would now indicate a recent myocardial infarction of the posterior wall. 18th day after admission: There is left axis deviation. S-T_1 and S-T_2 are depressed. S-T_3 is elevated. T_1 inverted and T_2, T_3 and T_{4F} upright. The record indicates marked myocardial damage.

Autopsy: #17861 (May 8, 1942). The body was that of an obese colored woman. The features of interest in the post-mortem examination were confined to the heart and aorta.

The pericardial sac was not distended and contained about 50 cc. of liquid blood. There was some clot around the pulmonary conus and the root of the aorta which was slightly adherent.

Heart and Aorta: The heart showed considerable hypertrophy, most marked in the left ventricle, and some dilatation; it weighed 600 gms. The right coronary artery appeared normal exteriorly, whereas the left showed some discoloration from blood within its wall for a distance of about 2 cm. from its origin. This discoloration extended beyond the point at which it divided into anterior descending and circumflex arteries and was particularly noticeable for a distance of almost 1 cm. along the course of the anterior descending artery.

The epicardium was roughened over a portion of the left ventricle. The mitral valve was slightly thickened and the base of the posterior

cusp of the aortic valve was calcified, producing a slight stenosis of the aortic ring. The coronary arteries showed a moderate degree of arteriosclerosis with rather diffuse involvement of the intima. At no place were they narrowed by this change, nor was any thrombus present in the lumen.

About 1 cm. above the sinus of Valsalva, there was a transverse rent in the intima of the aorta, 5 cm. in length. This led to a cavity between outer and inner coats of the aortic wall produced by a split in the media. The cavity extended around the sinus of Valsalva, and down to the aortic ring. The dissection extended along the left coronary artery and the anterior descending branch for a distance of 1 cm. beyond the origin of the latter and for a shorter distance along the circumflex branch. The aneurysm in the coronary wall was filled with a thrombus which occluded the vessel by compressing its lumen. There was no thrombus within the lumen. An extensive fresh infarction of the muscle supplied by the anterior descending artery could be seen grossly as an area lighter than normal and containing many red and yellow spots, and there were patches of fibrinous exudate on the epicardial surface.

The aortic dissection extended distalward over the arch of the aorta and continued down into the right iliac artery. It extended along the course of the celiac axis for a few mm., compressing but not occluding this vessel. On the exterior surface of the aorta just inside the pericardium was a mass of organizing hemorrhage, at the site of a small rupture in the outer wall of the aneurysm.

The remainder of the post-mortem examination showed no important abnormalities.

Microscopic Examination: Sections of the myocardium showed the alterations characteristic of infarction. Necrotic muscle fibres were bordered by polymorphonuclear leucocytes and hemorrhage. Many of the leucocytes were themselves necrotic and fragmented. In places, there was a hemorrhagic epicardial exudate that was beginning to be organized.

A section of the aortic wall just proximal to the rent in the intima showed that the dissection had split the media in its outer portion so that only a thin portion of the media was included in the outer wall of the aneurysm. A section from the root of the aorta, just inside the

FIG. 1. Distal portion of the dissection of the anterior descending branch of the left coronary artery, showing the presence of blood between the layers of the media.

FIG. 2. Section from left ventricle showing the infiltration of polymorphonuclear leucocytes between necrotic and dying muscle fibers at the margin of the infarction.

pericardial cavity and at the site of the hemorrhage into the pericardial sac, showed blood clot on the outer side of the adventitia but the actual point of rupture was not evident in the section.

A section of the anterior descending coronary artery, cut longitudinally, as the artery had been opened before the section was made, showed separation of the media by the hemorrhage which served to occlude the lumen.

DISCUSSION

At the bedside the problem appeared straight-forward enough and seemed clearly to be the differentiation between acute coronary thrombosis and dissecting aneurysm. The patient was forty-two years of age but had a marked degree of hypertension and there was definite sclerosis of the retinal vessels and even hemorrhages were found in one eye. The heart was also enlarged and there was evidence of a mild degree of failure.

The patient's age was somewhat younger than is commonly seen in dissecting aneurysm but a review of the literature reveals a surprising number of instances in comparatively young individuals. Klotz and Simpson (7) were able to collect forty-two instances in persons under forty years of age. Likewise, it is a much more common occurrence in men than in women. Shennan (8) found in his analysis of 300 cases that 65% were in males and that the percentage rose in males after 50 years of age. The same sex ratio obtains in coronary thrombosis. However, an elevation of the blood pressure does play a very significant role in dissecting aneurysm and the incidence of the latter is closely parallel to that of degenerative vascular lesions. It is quite clear from the reported cases that dissecting aneurysm seldom occurs in the absence of hypertension or degenerative disease of the aorta, and Weiss (3) goes so far as to say that it is doubtful that spontaneous rupture ever occurs in a normal aorta.

Pain, so conspicuous in both conditions, was very much in evidence here. It was sudden in onset, so characteristic of dissecting aneurysm. Although the pain of coronary thrombosis may be sudden in onset, it frequently is oppressive and constrictive rather than sharp and knife-like and tearing in character; it usually occurs at rest, even in sleep. The pain of dissecting aneurysm, on the other hand, characteristically

occurs with exertion, as it did in the present case. The location of the pain here was lower than is usual in dissecting aneurysm. It is commonly high in the chest rather than under the lower half of the sternum or in the epigastrium. Its location did, therefore, suggest coronary thrombosis more strongly. Its radiation to the back, however, was quite characteristic of dissecting aneurysm; it was intense under the right shoulder blade.

In the present case, the heart was greatly enlarged as one would expect with the degree of hypertension present. Such enlargement is of no real aid in the differential diagnosis. It is not uncommon to find hypertension with arteriosclerosis and coronary artery arteriosclerosis in both coronary occlusion and dissecting aneurysm. The absence of cardiac enlargement would be of considerable importance as the heart may be normal in size in coronary artery arteriosclerosis, whereas it is distinctly unusual to have a dissecting aneurysm without sustained hypertension and its resulting cardiac enlargement.

There was a mild degree of heart failure present in this case which progressed. This would strongly suggest myocardial damage as one would anticipate with myocardial infarction. One would not expect heart failure in dissecting aneurysm unless a high degree of aortic insufficiency had developed, when the additional burden of incompetent aortic leaflets might be sufficient to cause the heart to fail. The development of aortic insufficiency is a most important occurrence, and when one can be sure that it develops following the acute episode of chest pain, it is practically diagnostic of dissecting aneurysm. It often occurs in this condition, usually only shortly before the final rupture of the aneurysm into the pericardial sac, and may vary from simply the appearance of a diastolic murmur to a severe degree of aortic insufficiency with all of the signs in the peripheral circulation. In the present case there was no question about the appearance of a blowing diastolic murmur three days before death and a significant fall in the blood pressure to 150/60. The peripheral signs did not develop; however, the development of an aortic diastolic murmur under these circumstances left little doubt that a rupture of the aorta had occurred and that it had dissected down to the aortic ring. Furthermore, it indicated that final rupture into the pericardial sac was probably impending.

The mechanism by which aortic insufficiency is produced by dis-

secting aneurysm with a normal aortic valve, as is invariably disclosed at post mortem, has long been the subject of discussion. In 1925, Resnik and Keefer (9) ascribed the signs of insufficiency to the rapid escape of blood forward into the aneurysmal sac, but subsequently in the case reported by Hamman and Apperly (10) the small size of the aneurysmal sac seemed very definitely to preclude this possibility. They suggest improper closure of the aortic leaflets and further elaborate upon this point by advancing the idea that the presence of the hematoma within the aortic wall interfered with the proper contraction of the aortic ring. The alteration in the inner contour of the aortic ring by the pressure of the hematoma would distort the ring sufficiently to prevent apposition of the leaflets in the same plane and thereby mechanically produce an insufficient closure. It is at the aortic ring, where the pericardium is reflected up over the aorta, that rupture into the pericardial sac occurs. When this perforation is large and admits a large volume of blood into the pericardial sac, cardiac tamponade rapidly results and death is sudden. Frequently the rupture is small and only a leak develops, slowly admitting blood to the pericardial sac as occurred in the present case.

The diagnostic value of an aortic diastolic murmur, developing with or without the peripheral signs of aortic insufficiency in the course of protracted chest pain, cannot be over-emphasized for it is the best evidence we have that we are dealing with a dissecting aneurysm. Of course, the termination of dissecting aneurysm may be in some other manner; the dissection may not rupture into the pericardial sac and be the cause of death. But when such a chain of events occurs, termination by rupture into the pericardium is most likely. One must not fall into the error of interpreting the reappearance of a diastolic aortic murmur after the attending shock has disappeared as the initial appearance of the murmur. This is an unusual circumstance but one not easy to interpret. However, aortic diastolic murmurs produced by syphilis usually have given such pronounced evidence of the disease that this error is not likely to occur. Syphilis has never been thought to play any part in the development of dissecting aneurysm and in another case reported by Weiss (3), it was quite evident that syphilis, by fusion of the layers of the aorta, resisted the progress of a concomitant dissecting aneurysm.

The electrocardiographic changes seen at times in dissecting aneu-

rysm are the features most likely to confuse and lead one astray. Those occurring with myocardial infarction, when definite, are so characteristic and their association with coronary artery occlusion in various locations is so well established as to leave little room for doubt as to their interpretation. However, in dissecting aneurysm, variations from the normal electrocardiographic pattern frequently occur, often so closely simulating those characteristic of coronary artery occlusion that confusion readily arises. In many of the reported cases, electrocardiographic changes have been present but the inconstancy of the change present and the lack of change truly characteristic of coronary lesions have been the rule. In the case reported by Lawrence (4) the T waves were inverted in the first and second leads. The first case of Osgood, Gourley and Baker (11) showed inversion of the T wave in Leads I and II and depression of the S-T segment in the first lead. Later, a high take-off of the S-T segment appeared in Lead III, all of which was very suggestive of a recent coronary occlusion. Their second case likewise showed a diphasic T wave in Lead I, a depressed S-T segment in Lead I, and a high take-off of the S-T segment in Lead III. In 1940, Reisinger (5) reported a case in which progressive electrocardiographic changes occurred over a period of three months, varying from slight elevation of the S-T segment in Lead I to deep inversion of the T waves in the first and second leads. In the absence of myocardial infarction, it is at times difficult to understand how these electrocardiographic changes come about. When there is slow leaking into the pericardial sac and inflammatory reaction and adhesions ensue, one can understand how they are probably produced. Such changes doubtless account for many of the electrocardiographic alterations observed. But we see electrocardiographic changes in dissecting aneurysm frequently before we have clinical evidence that the pericardium has become involved and at autopsy do not always find ready explanation for these changes. A careful analysis of these cases would probably show that these are the minor electrocardiographic variations observed and not those confused with the changes of myocardial infarction. It is altogether possible that in the course of the dissection, coronary flow is interfered with sufficiently to cause electrocardiographic changes which are variable. The interference is, however, not sufficiently sustained to cause death of the muscle cells. The case of

Bayley and Monte (6) would support this view and their explanation of an acute local myocardial ischemia seems the most reasonable view to take.

The electrocardiographic changes in the present case led to great confusion as they seemed to indicate early in the period of observation a recent anterior myocardial infarction. There was progressive alteration which later seemed to indicate infarction of the posterior wall and finally changes indicative of extreme myocardial damage were present. The clinical impression was a dissecting aneurysm which was made definite by the appearance of an aortic diastolic murmur not previously present. It was difficult then to explain the evidence which seemed so clearly to indicate myocardial infarction and we were not able to postulate what had actually happened. It was new in our experience to have myocardial infarction develop from a dissecting aneurysm. But when one sees the mechanism by which it may be produced, the wonder is that the dissection does not more often proceed along a coronary artery and the pressure of the hematoma against the inner layer of the artery occlude it. It evidently is an infrequent occurrence and the case described by Weiss is the only similar one of which we are aware*. Probably it has occurred more often and has escaped attention. A course of events such as is described should suggest the possibility and I have no doubt that it can be correctly predicted clinically.

SUMMARY

A case of dissecting aneurysm is presented in which myocardial infarction was produced by dissection along the left coronary artery and its anterior descending branch. The lumen of the latter was occluded by the pressure of the hematoma within its wall. The clinical features of the case were those of both dissecting aneurysm and myocardial

* Since the submission of this report for publication Case No. 28072, of the Case Records of the Massachusetts General Hospital, recorded in the New England Journal of Medicine, *226:* 273, 1942, has come to the author's attention. In this case the dissection of the aorta involved "the mouths of both coronary arteries and that of the innominate artery." Dr. Alfred O. Ludwig's clinical prediction was, "I believe that the post mortem examination will disclose . . . multiple dissecting aneurysms encroaching on the vessels of the arch, the coronary arteries and possibly the renal arteries."

infarction. When typical signs and symptoms of both conditions are present, such a course of events as obtained here warrants clinical consideration and probably occurs with greater frequency than reports indicate.

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THE INFLUENCE OF A NUMBER OF ANDROGENIC STEROIDS ON THE URINARY EXCRETION OF NEUTRAL 17-KETOSTEROIDS[1]

ELIZABETH G. FRAME, WALTER FLEISCHMANN AND LAWSON WILKINS[2]

Associated with a study of the effects of the administration to dwarfed boys of a number of steroids having an androstene or androstane nucleus on creatine and nitrogen metabolism, the results of which are being published elsewhere (1), observations have been made also on the excretion of 17-ketosteroids. The literature on the effects of androgen treatment on androgen and 17-ketosteroid excretion has been reviewed by Koch (2). In brief, and confining our review to 17-ketosteroid excretion, the following pertinent data have been reported in the literature. The administration of testosterone propionate leads to an increased total 17-ketosteroid excretion (2, 3), and specifically to an increased excretion of androsterone and etiocholanolone-(*3α,17*) (Callow (4); Dorfman (5, 6)), and of isoandrosterone (7). Further, Dorfman (8) and Dorfman and Hamilton (9) found that the administration to eunuchoid men of androstanediol-(*3α,17*), androstanedione-*3,17* and of Δ 4-androstenedione-*3,17* each led to an increased excretion of androsterone. In those cases where the pure compounds have been isolated from the urine the recoveries have been low as compared with the theoretical yields. In contrast with the increased 17-ketosteroid excretion following the administration of the above steroids there exists considerable evidence to indicate that the androgenic steroid, methyl testosterone, is not excreted as a 17-ketosteroid (9, 10, 11).

The present study confirms the results of previous investigators on the effects on 17-ketosteroid excretion of the administration of different

[1] This work was made possible by a grant from the Commonwealth Fund for the study of endocrine problems in childhood, supplemented by the John Howland Memorial Fund.

[2] From the James Buchanan Brady Urological Institute and the Harriet Lane Home of the Johns Hopkins Hospital, and the Departments of Urology and Pediatrics of the Johns Hopkins University.

androgenic steroids, and presents the results of the administration of 4 additional steroids which have not hitherto been reported. The use of dwarfed, sexually retarded boys, with very low urinary 17-ketosteroids before treatment, as subjects affords certain advantages in that the possible complication of obscuring the effect of steroid administration by lowering the body's production of 17-ketosteroids is reduced to a minimum.

TABLE I

Effects of various steroids causing an increased 17-ketosteroid excretion

COMPOUND	NO. CASES	DOSE*	ROUTE ADM.	TREATMENT	17-KETOSTEROIDS*			
					Before treatment	During treatment	Increase	Recovery†
		mg./24 hrs.		*days*	*mg./24 hrs.*	*mg./24 hrs.*	*mg./24 hrs.*	%
Androsterone	1	20	i.m.	8	1.9	7.3	5.4	27
Dehydroisoandrosterone	1	20	i.m.	14	1.9	7.6	5.7	29
Δ4-Androstenedione-*3,17*	1	20	i.m.	10	1.2	7.4	6.2	31
Testosterone	2	20	i.m.	6	2.3; 5.8	9.7; 12.1	7.4; 6.3	37; 32
Testosterone propionate	7	8.4–21	i.m.	5–15	1.0–3.9 (av. 2.2)	2.5–12.2 (av. 9.2)	1.5–8.3 (av. 5.8)	18–52 (av. 35)
Δ5-Androstenediol-(*3β, 17α*)-diacetate	2	22.5; 33.8	i.m.	8; 13	3.0; 5.0	18.6; 12.3	15.6; 7.3	69; 32
Androstanediol-(*3α, 17α*)-diacetate	2	22.5; 30	i.m.	14	3.4; 3.1	8.1; 8.4	4.7; 5.3	21; 18

* Calculated as androsterone.

† Per cent of amount administered per 24 hrs.

PROCEDURE

The subjects were sexually underdeveloped male dwarfs ranging in age from 9 to 18 who were hospitalized throughout the course of the study. They received a diet which was constant in respect to the content of protein, carbohydrate and fat and contained no meat or fish. The steroids[3] were administered either orally or intramuscularly or by

[3] The authors are indebted to Drs. E. Oppenheimer and C. R. Scholz of Ciba Pharmaceutical Products, Inc., Summit, N. J., for supplies of the steroids.

both routes, as specified in Tables I and II. Twenty-four hour urine collections were made at varying intervals before and during treatment. The urine was collected in bottles containing 10 cc. concentrated hydrochloric acid, and the procedure of extraction and determination of the total neutral ketonic 17-ketosteroids was carried out according to the method outlined by one of the authors (12), using the absolute alcohol technique of the Zimmerman colorimetric reaction. Separation into alpha and beta fractions, using the above method, was performed on only one specimen, that of a case 20 days after the administration of Δ 5-androstenediol-(*3β,17α*).

TABLE II

Effect of various steroids causing no significant increase in 17-ketosteroid excretion

COMPOUND	NO. CASES	DOSE*	ROUTE ADM.	TREATMENT	17-KETOSTEROIDS*			
					Before treatment	During treatment	Increase	Recovery*
		mg./24 hrs.		*days*	*mg./24 hrs.*	*mg./24 hrs.*	*mg./24 hrs.*	%
17-Methyl-testosterone	6	10–24	oral	6–150	1.2–4.7 (av. 2.6)	1.1–4.4 (av. 2.2)	0–0.9	0–4
	1	19	i.m.	16	3.2	1.3	0	0
17-Methyl-Δ5-androstenediol-(*3β, 17α*)	5	29–48	oral	12–27	1.2–4.6 (av. 3.1)	2.1–5.2 (av. 3.6)	0–2.1	0–7
	2	29–48 + 10	oral + i.m.	29; 27 + 13; 2	3.1; 4.6	7.9; 4.0	0–4.8	0–8
17-Methyl-androstanediol-(*3α, 17α*)	1	29	oral	28	3.3	4.3	1.0	3
	1	38–48	oral	13	5.6	8.7	3.1	6
17-Ethyl testosterone	3	18–46	i.m.	6–20	1.9–5.3 (av. 3.5)	1.6–6.1 (av. 3.7)	0–0.8	0–4

* Legends as in Table I.

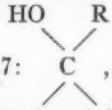
RESULTS AND DISCUSSION

The results are summarized in Tables I and II. The values given for the 17-ketosteroid excretion before treatment represent in most cases the average value of several separate determinations. The figures included in the columns 'during treatment' are typical of several values obtained at different periods after the treatment had started.

In some cases the total period of treatment was longer than that indicated in the tables. In order to estimate the quantitative recovery, the administered steroids as well as the urinary 17-ketosteroids are calculated as androsterone.

In Table I are included the 6 steroids the administration of which is accompanied by an increase in the urinary 17-ketosteroids. Three of these compounds, androsterone, dehydroisoandrosterone and Δ 4-androstenedione-(*3,17*), are 17-ketosteroids. Of 20 mg. administered per 24 hours about 30 per cent is recovered on the 8th to the 14th day, indicating that a portion of these compounds is excreted, if not unchanged, at least in a form similar in structure to the administered compound. The 3 remaining compounds in Table I, testosterone (free or as the propionate), Δ 5-androstenediol-(*3β,17α*)-diacetate, and androstanediol-(*3α,17α*)-diacetate, possess a free or esterified hydroxyl group in the 17 position. The finding that a significant percentage (18–69%) of these compounds is recovered in the urine as 17-ketosteroids indicates that the body is capable of hydrolyzing the esters and of oxidizing the 17-hydroxy- to a 17-keto- compound. The percentage recoveries of testosterone and testosterone propionate are in the same range as where the compound administered was a 17-ketosteroid. There is no obvious explanation for the high recovery in one case after the administration of androstenediol diacetate, or for the lower recovery after androstanediol diacetate. Probably no significance should be attached to such variations in recovery on single isolated days, since the normal day to day variation in 17-ketosteroid excretion is known to be considerable. In Figure I typical individual cases on different treatments are represented graphically.

The compounds listed in Table II all contain the following grouping at C atom 17:



, where R represents a methyl or ethyl group. The administration of these steroids is not accompanied by a significant increase in the 17-ketosteroid output, and in some cases there is a decrease. For this reason the 17-alkyl androgenic steroids are valuable agents in the study of the effects of androgen administration on the endogenous production of urinary 17-ketosteroids. The administra-

tion of these steroids in most cases was accompanied by no increase in the output of 17-ketosteroids. In a few cases there were slight increases which did not exceed 8% and may be within the errors of the method. Albright (13) has detected a fall of 17-ketosteroids in Cushing's syndrome during treatment with methyl testosterone, making use of the fact that this compound is not itself excreted as a 17-ketosteroid. It appears probable from the present results that the first step in the

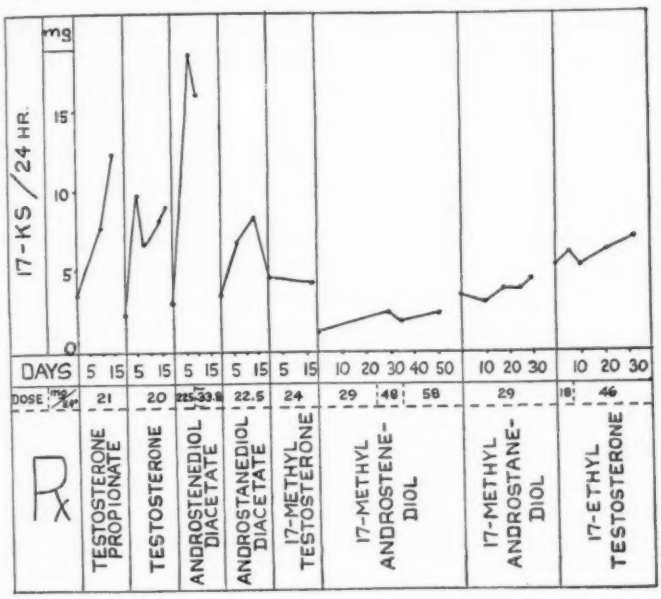


FIG. 1

metabolism of these compounds is not the removal of the alkyl group at C atom 17, since little, if any, of the administered steroid was recovered as a 17-ketosteroid. Although 17-methyl testosterone is extensively used clinically as an androgen, no data are available as yet on its metabolic products.

The single specimen which was separated into alpha and beta components was that from a case which had been treated with Δ 5-androstenediol, (*3β*,*17α*)-diacetate for 20 days. From a pre-treatment level

of total 17-ketosteroid excretion of 5.0 mg. per 24 hours the output increased to 12.8 mg. of which 16.4 per cent was present in the beta form. Unpublished data by one of the authors (E. G. F.) have shown that in normal individuals 1–4 per cent of the total neutral ketonic 17-ketosteroids is present in the digitonin-precipitable (3-beta-hydroxy-) fraction. The present case, therefore, represents a relatively high proportion of the 3-beta compound, as might be expected from the fact that the administered compound was a 3-beta-hydroxy-steroid. The failure to obtain a higher recovery of the beta compound may well be explained by its alteration in the process of hydrolysis.

SUMMARY

Eleven different steroids having an androstane or androstene nucleus were administered to dwarfed boys and the effects on the neutral 17-ketosteroid excretion determined.

The administration of the following compounds was accompanied by a significantly increased excretion of 17-ketosteroids: testosterone (free or propionate); androsterone; dehydroisoandrosterone; Δ 4-androstenedione-(*3,17*); Δ 5-androstenediol-(*3β,17α*)-diacetate; and androstanediol-(*3α,17α*)-diacetate.

The urinary 17-ketosteroids were not increased by the administration of the following compounds: 17-methyl testosterone; 17-methyl Δ 5-androstenediol-(*3β,17α*); 17-methyl-androstanediol-(*3α,17α*); and 17-ethyl testosterone. For this reason the 17-alkyl androgenic steroids are valuable agents in the study of the effects of androgen administration on the endogenous production of urinary 17-ketosteroids.

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RIBOFLAVIN DEFICIENCY IN SWINE[1]

With Special Reference to the Occurrence of Cataracts

MAXWELL M. WINTROBE,[2] WILHELM BUSCHKE, RICHARD H. FOLLIS, JR. AND STEWART HUMPHREYS[2]

From the Departments of Medicine and Ophthalmology, Johns Hopkins University

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The discovery of a number of components of the vitamin B complex has made necessary a revaluation of the effects of B complex deficiencies which at one time were attributed to the lack of certain vitamins. When we found that good growth and normal appearance and activity occurred in pigs given a highly purified diet supplemented with crystalline thiamine chloride, riboflavin, nicotinic acid, pyridoxine hydrochloride, choline chloride, and calcium pantothenate (28), experiments were undertaken to study the effects produced when only one of these vitamins is omitted from the dietary supplements. The addition of inositol and of p-aminobenzoic acid to these six vitamins has made no noticeable difference in the growth or well being of our animals (unpublished data). It is true that this mixture of crystalline vitamins does not include biotin, "folic acid" or other less well defined components of the B complex but a need for these factors has not been observed under the conditions of our experiments. Consequently it seems justifiable to assume that when of the above crystalline vitamin supplements, one vitamin is omitted, the changes occurring are in all likelihood attributable to the lack of that vitamin.

Descriptions of thiamine (30, 7, 24), pyridoxine (16, 2) and pantothenic acid (25) deficiency in swine have already appeared from this laboratory and a report of the role of nicotinic acid in the nutrition of the pig is in preparation (29).

Using a diet which was probably inadequate in other factors as well as riboflavin, Hughes (10) noted impaired growth, diarrhea, and abnor-

[1] These studies were aided by grants from the Rockefeller Foundation, Parke-Davis and Company, and the Upjohn Company, and were carried out in cooperation with the Bureau of Animal Industry of the U. S. Department of Agriculture.

[2] Present address, School of Medicine, University of Utah, Salt Lake City, Utah.

mal gait. Later he concluded (11) that the minimum requirement for riboflavin in the young growing pig lies between 1 and 3 mg. per 100 pounds weight (22 and 66 micrograms per kilogram body weight). Patek, Post, and Victor (15) observed impaired growth, a decline of body temperature, cloudiness of the cornea, changes in the skin, hair, and hoofs, and a terminal collapse associated with hypoglycemia. The cloudiness of the cornea cleared partially after adminstration of riboflavin. A dense central opacity in the optical media was observed following clearing of the clouding. Its location was not definitely defined as being in the lens, although Patek and his associates referred to this opacity as resembling a cataract. A "flat footed" gait was noted which was attributed to muscle weakness or tendon relaxation. There was no loss of appetite or diarrhea, and there were no neurological symptoms until the onset of collapse. Anemia and spastic paralysis which developed later, and adrenal hemorrhages found at autopsy, were attributed to the lack of food factors other than riboflavin.

To our knowledge the only report of riboflavin deficiency in pigs fed a purified diet probably adequate in other respects is the statement in the Yearbook of Agriculture, 1942, where mention is made of observations at the Bureau of Animal Industry, U. S. Department of Agriculture (13). Impaired growth, frequent vomiting, severe diarrhea, rough skin and hair coat, considerable secretion about the eyes and a peculiar gait are described. In a further statement referring to this work, Ellis, Madsen and Miller (6) indicated that incoordination occurred in 2 out of 4 pigs fed a purified diet supplemented with thiamine, niacin, choline, pyridoxine and calcium pantothenate. Histologic changes were noted in the sciatic nerve in 3 of the animals and in the spinal cord in 1. No details are given.

Our own failure previously (28) to produce riboflavin deficiency in the pig can be accounted for by the presence of riboflavin in the crude casein which forms 26.1 per cent of our standard basal diet. The pigs in the above mentioned experiments probably received as much as 40 micrograms of riboflavin per kilogram body weight through this medium. A repetition of the experiment using vitamin-free casein was therefore planned. Although the number of animals is small, it is thought desirable to record these studies, particularly in view of the ophthalmological observations.

EXPERIMENTAL PROCEDURE

The general management of the pigs was similar to that described in previous reports (28). The basal diet consisted of casein, 26.1 per cent; sucrose, 57.7 per cent; lard, 11.0 per cent; and a complete mineral mixture (27), 5.2 per cent. Instead of Sheffield "New Process" casein, however, SMACO vitamin-free casein was fed. This basal diet was supplemented with cod liver oil, 0.5 grams per kilo per day, and the following crystalline vitamins were fed by capsule:

Thiamine hydrochloride	0.52 mg. per kg. body weight daily
Nicotinic acid	1.20 " " " " " "
Pyridoxine hydrochloride	0.20 " " " " " "
Choline chloride	10.00 " " " " " "
Calcium pantothenate	0.50 " " " " " "
Inositol	1.20 " " " " " "
p-Aminobenzoic acid	0.50 " " " " " "

OBSERVATIONS

Signs of nutritional deficiency became apparent within two to three weeks. The animals failed to gain in weight, they began to lose their normal well-rounded appearance, and their coats, at first clean, smooth and tidy, became dirty and unkempt. Occasionally diarrhea appeared, but lasted only a day or two. In one pig (7-77), the gait was noted to be unusual as early as eighteen days after the experimental deficiency was commenced. This pig died suddenly sixteen days later before other signs of nutritional deficiency became clear. Pigs 7-75 and 7-76 lived more than three months longer, and in these pigs markedly impaired growth, changes in the skin and eyes, anemia, and abnormal gait developed.

In figure 1 the *growth* of these three pigs is compared with that of two litter mates which were fed the same basal diet, including vitamin-free casein, but supplemented with riboflavin (0.12 mg. per kg. body weight daily). These two pigs (7-73 and 7-74) were given no nicotinic acid, but this did not impair their growth rate (29).

Comparison is also made in figure 1 with the growth of three pigs (6-57, 6-61, 6-78) fed a basal diet containing vitamin-free casein obtained from another source (Sheffield By-Products Co.) and supplemented with riboflavin and nicotinic acid as well as thiamine, pyridox-

ine hydrochloride, choline chloride, and calcium pantothenate in the amounts already stated.

The *hair coats* of pigs 7-75 and 7-76 became rough, dry and thin, and the hair seemed to come out readily. On the skin a mottled, erythem-

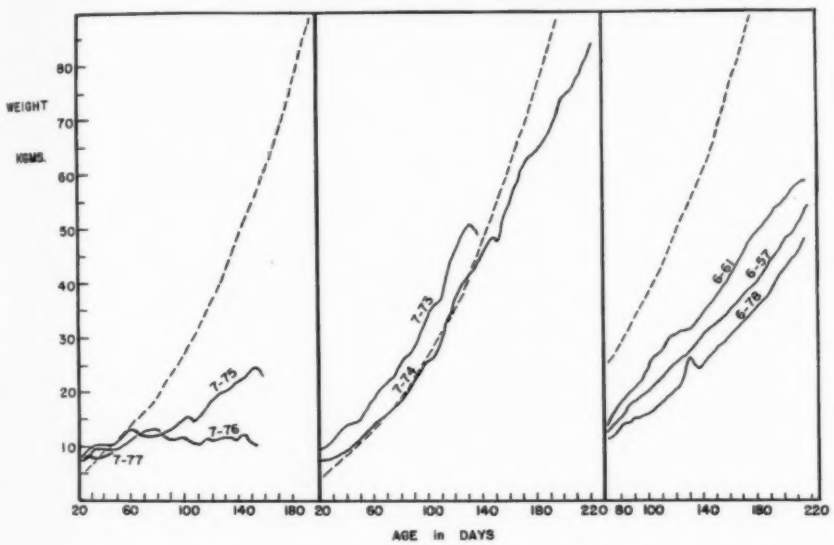

FIG. 1. GROWTH OF THREE PIGS (7-75, 7-76, 7-77) FED A DIET LACKING IN RIBOFLAVIN, COMPARED WITH THAT OF LITTER MATES (7-73, 7-74) FED A SIMILAR DIET LACKING NICOTINIC ACID RATHER THAN RIBOFLAVIN

The third group of growth curves (pigs 6-57, 6-61, and 6-78) is that of pigs fed a similar diet which included both of these vitamins, as well as thiamine, pyridoxine, choline, and pantothenic acid. These, however, were not litter mates of the first two groups and the experimental diet was commenced at a later age.

The broken line, shown for comparison, represents the growth of pigs given a mixed diet at the Beltsville Research Center and fed and handled according to record of performance procedure.

atous eruption appeared. This was most noteworthy on the snout, behind the ears, along the midline of the back and in the adjoining regions of the skin, in the area of the groin and over the abdomen. The affected skin became scaly, and reddish brown scabs formed. About

the hoofs ulceration developed. The horn of the hoofs became thickened and ridged and the adjoining skin was broken and covered with a bloody exudate.

The eyelids appeared swollen and *lens opacities* developed. The latter were seen in pig 7-75 when it was 112 days of age, 91 days after institution of the deficient diet. The lens changes were first observed *in vivo* with the ophthalmoscope, using the Friedenwald hand slit-lamp, and a few days later could be seen even with the naked eye. At this time, for further study, one eye was enucleated under ether anesthesia after maximal dilatation of the pupil. The eye was examined immediately with the slit-lamp. There was an outspoken separation of the lens fibers both in the anterior and in the posterior cortex, particularly in the subcapsular regions. Many fine white dot and streak opacities and a few minute vacuoles were visible in the anterior cortex and at the anterior lens pole. A dense, white wave-like opacity was present near the equator of the lens. The deep cortex and the nucleus were entirely clear (figure 2). The cornea was clear and showed no vascularization. The second eye of the same pig was punctured and the aqueous humor was examined for ascorbic acid, since it is known that the ascorbic acid level of the aqueous is decreased in several conditions in which there is lens damage (14). The ascorbic acid level of the aqueous was 14 milligrams per cent; that is, normal. This animal was sacrificed at 162 days of age. By that time the superficial anterior and posterior lens cortex of the remaining eye were densely opaque.

In the second pig (7-76), lens opacities were not seen during life. This animal died at 156 days of age, 135 days after institution of the riboflavin-deficient diet. The eyes had not been examined during life in the preceding three weeks. Dissection of the eyes, approximately twenty-four hours after death, and direct examination of the lenses revealed the same type of cortical opacities which had been seen in pig 7-75 (figure 2). Under the dissecting microscope, the equatorial opacities appeared as yellowish globular masses in the superficial cortex; a few vacuoles and glassclear spokes were seen near the equator.

The histological examination of the remaining parts of the eyes of this animal and of the second eye of pig 7-75 did not reveal pathological changes.

Appetite was maintained quite well, the pigs consuming a full unit

of diet (36.4 grams basal diet per kg. body weight daily) with rare exceptions. Diarrhea occurred from time to time, but was not persistent. The failure to gain weight at a normal rate in spite of good consumption of a diet furnishing approximately 152 calories per kilo and permitting good growth in other animals, suggests poor food utilization in riboflavin deficiency.

FIG. 2. CATARACT IN RIBOFLAVIN DEFICIENCY IN A PIG
(SLITLAMP COMPOSITE DRAWING)
Insert: Photograph of the same eye, showing the equatorial opacities

Pig 7-77 died before anemia developed, but in the remaining two a slowly progressive, normocytic anemia of moderate degree occurred (figure 3). No other significant changes in the blood were observed.

The *gait* of the pigs appeared stiff, mincing and hesitant. An abnormal gait was first noted after four weeks on the experimental diet in pig 7-76 and after six weeks in 7-75. The "goose-stepping", inco-

ordinated gait of pantothenic acid- and pyridoxine-deficient pigs (28) was not seen. The "flat-footed" gait described by Patek *et al.* (15) was not observed. In fact, at times the pigs appeared to be walking on the tips of the hoofs.

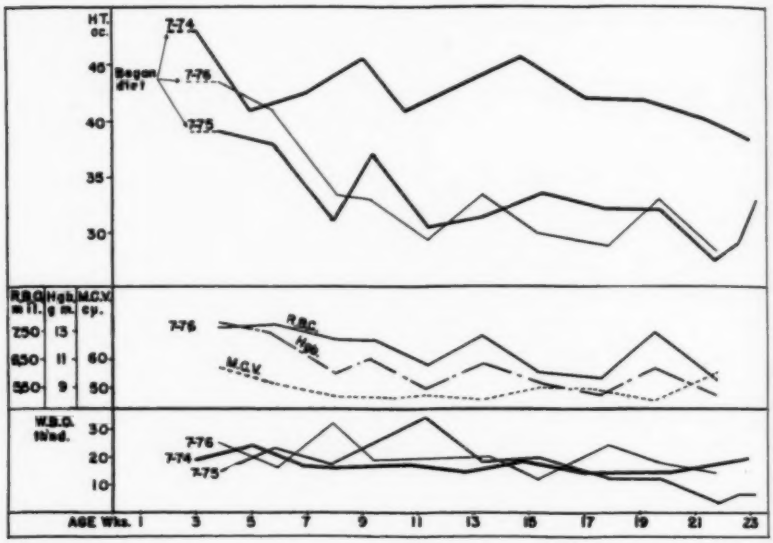

FIG. 3. SHOWING THE DEVELOPMENT OF ANEMIA IN TWO RIBOFLAVIN-DEFICIENT PIGS (7-75 AND 7-76)

Pig 7-74 was a control animal

In the uppermost section the development of anemia is indicated by the decreasing volume of packed red cells (Ht.). In the middle section details of red cell count (R.B.C.), hemoglobin (Hgb.) and mean corpuscular volume (M.C.V.) in one animal are shown. The anemia was essentially normocytic or only slightly microcytic.

In the lowest section the leucocyte counts (W.B.C.) are shown.

Pig 7-75, when 162 days of age, was found unable to stand or to eat. It was sacrificed for autopsy examination. Pig 7-76 was found dead at the age of 156 days after having been extremely weak for about ten days.

Electrocardiograms were made from time to time but no significant abnormalities were noted.

PATHOLOGIC FINDINGS

Pig 7-75

This pig was killed after 145 days on the deficient diet. The liver was pale, not distinctly yellow but enlarged, weighing 1000 gms. Each kidney weighed 100 gms. and was extremely pale. The other organs were not remarkable.

Microscopically, the peripheral nerves, ganglion cells, and spinal cord showed no change. A great deal of fat was found in the liver where it appeared as droplets of varying size in the cells of the peripheral portions of the lobule. In the cells of the renal convoluted tubules there was a great deal of fat which appeared as small and large droplets. There were foci of necrotic fibers in the myocardium of the left ventricle and a few in the right as well. The auricles appeared normal. A few smaller necroses were found in a section of skeletal muscle. The esophagus showed an early ulcer together with more superficial inflammation of the mucosa elsewhere.

Pig 7-76

This animal died after being on the deficient diet for 135 days. Very little was found grossly at autopsy to explain its death. The liver weighed 340 gms. and each kidney weighed 50 gms.

Demyelinization was found in both the brachial and sciatic nerves. In both it was rather extensive. No definite chromatolysis was found in the cells of the dorsal root ganglia. The spinal cord was normal. In the convoluted tubules of the kidney there was a small amount of fat. The liver, tongue, and heart showed nothing abnormal. There was slight inflammation of the lining of the esophagus. In the voluntary muscle there were rather extensive areas of necrosis. Microscopically, there was no explanation as to the cause of death.

Pig 7-77

This animal died after being on the deficient diet for 34 days. At autopsy no lesions were found grossly to explain the pig's death. The liver weighed 340 gms. and the kidneys averaged 32 gms. each.

Microscopically, the peripheral nerves, dorsal root ganglia, and spinal cord showed no lesions. Sections of the liver, tongue, voluntary muscle and heart were not remarkable. In many of the convoluted

tubules of the kidney there were droplets of fat. Many collections of a large rounded fungus-like organism were found overlying and invading the epithelium of the esophagus. The epithelium showed a few areas of early ulceration and leukocytic infiltration. The same organism was found within lymphoid tissue of the intestine and in a small tubercle-like lesion in the spleen. A small ulcer containing the organisms was present on an eyelid. The cultural identity of the organism was not determined. However, it resembled Monilia albicans more than anything else. It is likely that this accounted for the death of the animal.

DISCUSSION

These observations are recorded because they present the effects of riboflavin deficiency in the pig, uncomplicated by other deficiencies. They indicate that lack of riboflavin in this animal produces effects similar to those observed in certain other species. In the *rat*, growth impairment, skin changes (22), and cataract (4) have been observed, and abnormal gait accompanied by degeneration of the myelin sheaths of the nerves, axis cylinder swelling and fragmentation, as well as myelin degeneration and gliosis in the spinal cord have been described (18). Similar changes in the nervous system of *chicks* have been reported (16). In the *dog*, dermatitis, muscular weakness of the hind quarters, conjunctivitis, vascularization of the cornea and corneal opacities, tachycardia, a collapse syndrome and fatty liver have been reported (17). Other workers (21), using tikitiki as the source of the water-soluble vitamins, described myelin degeneration of peripheral nerves and the posterior columns of the spinal cord. The deficiency in these animals was probably not simply one of riboflavin, for protection of control animals by giving riboflavin was not complete. Riboflavin deficiency in the *mouse* has been found by Lippincott and Morris (12) to be associated with greatly impaired growth rate, loss of hair, an atrophic and hyperkeratotic dermatosis associated with fissuring of the skin, keratitis and, infrequently, cataract, as well as ill-defined myelin degeneration in the spinal cord and the sciatic nerves. Waisman (23) has produced acute riboflavin deficiency in the *monkey*. This was characterized by growth failure, a "freckled" type of dermatitis appearing first on the face and in the area of the groin, incoordination of the limbs together with impairment of the grasping reflex, and severe

anemia. Waisman called attention to the absence of impairment of appetite, cheilosis and vascularization of the cornea.

The specific relation of riboflavin to cataract has been demonstrated in rats (5) by the prevention and arrest of the cataract when crystalline riboflavin was given. The thin cornea and shallow anterior chamber of the eyes of a small animal such as the rat, however, might conceivably *predispose* the rat's lens to cataract under the influence of exogenous physical damage (evaporation, temperature changes). It is important to know whether cataract will also develop in the eyes of larger animals as the result of riboflavin deficiency. Cataract was described in monkeys (3), but these animals were deficient undoubtedly in several factors of the B-complex, and, furthermore, the data which were published are inadequate for independent evaluation. The somewhat controversial literature concerning the experimental conditions under which this type of cataract has been observed in the rat, has recently been reviewed (1).

Throughout the period of observation of the riboflavin-deficient pigs, a litter mate (7-64) of pig 7-75, receiving quantitatively restricted stock diet (30), but adequately supplemented with crystalline B vitamins, including riboflavin, was examined. No changes were noticed in the eyes of this pig, even eight weeks after the death of the deficient pigs. Furthermore, the eyes of twenty-one comparable young pigs of breed similar to that of those under discussion were examined with the ophthalmoscope after dilatation of the pupil by atropine and ephedrine. With one exception, no eye changes were found. One of these young pigs showed a nuclear, apparently congenital opacity in the lens of one eye. The cataracts observed in our riboflavin-deficient animals were located in the superficial cortex, the part of the lens which is laid down after birth. Judging by this, and from the fact that the lenses were not abnormally thin, the cataracts in our animals were, no doubt, of recent origin.

In order to see how frequently cataract can be found at random in pig eyes, 178 eyes of pigs obtained at a neighboring slaughterhouse were bisected at the equator, the lenses removed in the capsules and examined. Of these 178 eyes, 12 had been stored without any preservative at room temperature in the open air for one day, and 25 others had been kept in saline for the same length of time. The remaining 141 eyes were examined a few hours after the animals had been killed.

None of these eyes showed any lens opacities similar to those seen in the riboflavin-deficient pigs. Two microphthalmic eyes were found, and the lenses of these eyes showed a disc-like posterior polar opacity. The appearance of these cataracts was quite different from that of the riboflavin-deficient animals.

It might be added that, in the course of the last five years, eye examinations of pigs receiving diets deficient in various fractions of the vitamin B-complex and of control animals have been made by us during life at frequent intervals. In no instance have lens opacities been observed except as above described.

Vascularization of the cornea was not observed in our animals.

Anemia developed in the two riboflavin-deficient animals which survived a long time. It was moderate in degree, gradual in progress, and normocytic in type, in contrast to the anemia occurring in pyridoxine deficiency (26, 2) which is microcytic in type, may advance rapidly, and may be very severe. György, Robscheit-Robbins and Whipple (8) presented evidence that the administration of riboflavin causes an increase in hemoglobin production above the basal level in standardized anemic dogs. Anemia has been described in the dog as a consequence of riboflavin deficiency (20). Severe anemia developed in Waisman's (23) riboflavin deficient monkeys. The present observations in the pig are in agreement with those reported for the dog and the monkey. It is noteworthy that, with one exception, none of the other pigs whose growth curves are shown in figure 1 developed anemia. In the one exception (7-73), a pig given no nicotinic acid, anemia of the type and degree seen in the riboflavin-deficient pigs was found, but in this animal a severe hoof infection had developed. We have observed anemia in association with infections in other pigs as well. In the pigs lacking riboflavin, however, no severe hoof infection was discovered at autopsy, and no cause for anemia was found other than the riboflavin deficiency. Leukopenia, such as that described in rats by Shukers and Day (19) as resulting from inanition, was not found in our animals although the leukocyte count at the time of death was low as compared with the initial values.

Further observations will be required to define the nature of the changes in the nervous system associated with riboflavin deficiency in the pig.

SUMMARY

Riboflavin deficiency in young pigs was associated with growth impairment, rough, dry and thin hair coats, a mottled, erythematous eruption together with scaling and ulceration of the skin, lens opacities, normocytic anemia and abnormal gait.

The cataracts were cortical, of identical appearance and of recent origin. No similar cataracts were seen on examination of a large number of normal pigs and of pigs deficient in B vitamins other than riboflavin.

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FURTHER EXPERIMENTAL CARDIAC LESIONS OF THE RHEUMATIC TYPE PRODUCED BY ANAPHYLACTIC HYPERSENSITIVITY

ARNOLD R. RICH AND JOHN E. GREGORY

(From the Department of Pathology, The Johns Hopkins University Medical School)

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We have recently described and illustrated the experimental production of cardiac lesions having the basic characteristics of rheumatic carditis (1). Those lesions, which were produced by hypersensitive reactions to foreign protein introduced intravenously, were situated in the heart valves, in the mural endocardium (particularly in the region of the valvular attachments, as in human rheumatic carditis), in the myocardium and in the pericardium; and they exhibited the basic, specific characteristics of rheumatic lesions, i.e., (a) lesions of the Aschoff body type, consisting of focal oedema, swelling and degeneration of collagen fibres with a marginal accumulation of large, often multinuclear cells, including the so-called "Anitschkow myocytes"; (b) inflammatory lesions that healed with scarring; (c) minute focal necroses of myocardial fibres. These lesions were produced by subjecting rabbits to anaphylactic reactions of the serum-sickness type.

In the above-mentioned paper it was pointed out in some detail that, in the human being, a wide variety of clinical and pathological manifestations are common both to rheumatic fever and to anaphylactic serum-sickness (*e.g.*, fever; arthritis; identity of character of rheumatic synovial exudate with that of serum-sickness arthritis; relief of arthralgia by salicylates; cardiac functional abnormalities; urticaria; erythemas; purpura; transient pareses; myocarditis; valvulitis; focal swelling and degeneration of cardiac collagen; cardiac tissue eosinophilia; inflammatory-necrotic arterial lesions). In a subsequent paper (2) we pointed out the fundamental identity of the peculiar rheumatic pneumonitis (capillary thrombosis and necrosis, focal inflammatory exudation, haemorrhage, hyaline membrane lining alveoli) with that of the pneumonitis resulting from anaphylactic hypersensitivity to sulfonamides in man.

These various circumstances were presented in support of the view that the lesions of rheumatic fever represent focal hypersensitive reactions to a foreign antigen, perhaps in most instances to some product of haemolytic streptococci. In our previous paper (1) we have referred to the literature relating to this possibility, which has, for some years, suggested itself to a number of students of the disease. We have continued the study of the tissue effects of experimental hypersensitive reactions, and we are engaged in an attempt to obtain information regarding the types of hypersensitivity of rheumatic patients to constituents of streptococci.

Because of the importance of any observations that may help to clarify the pathogenesis of the disabling rheumatic process, we have thought that it would be worthwhile to illustrate further the basic similarity between the lesions of rheumatic carditis and those that we have been able to produce experimentally by means of anaphylactic reactions. The purpose of the present paper, therefore, is to present a series of additional experimental lesions of the rheumatic type that have come under our observation since the publication of our previous paper. Some of these lesions represent material obtained from further sectioning of the hearts of our original series of animals; others are from subsequent experiments. The lesions here illustrated were selected from a far larger number of similar lesions.

The experimental method throughout has been that described in our first paper (1), and it need not be repeated in detail here. It consisted essentially in producing a serum-sickness type of reaction by the intravenous injection of foreign protein. In our first experiments we used sterile horse serum, without preservative. In subsequent experiments we have used horse serum in the same manner, and also a filtered saturated solution of Merck's powdered egg albumin in normal saline; and in one experiment we used the toxin of haemolytic streptococci as the sensitizing agent.[1] We have observed lesions following the treatment with horse serum more frequently than with either of the latter antigens. Of 51 rabbits treated with horse serum, cardiac lesions of the rheumatic type have been found in 19. In 14 of these 51 animals the region of the valves was not studied, for we were then

[1] The horse serum and the streptococcal toxin were kindly supplied by the Medical Research Division of Sharp and Dohme, Inc.

engaged in the experimental production of arterial lesions of the periarteritis nodosa type (5), and we were unprepared for the appearance of cardiac lesions of the rheumatic type. Since the valves and the region of their attachments are sites of predilection of the lesions of the rheumatic type in the experimental animal as in man, it is probable that more than 19 of the 51 serum-treated rabbits, developed the lesions. In contrast, cardiac lesions appeared in only 1 of 13 rabbits treated with egg albumin; and while 1 of 6 rabbits sensitized to streptococcal toxin developed the periarteritis nodosa type of arterial lesion, none showed cardiac lesions. Egg albumin is lost freely in the urine of the rabbits; and the streptoccoccal toxin failed to produce a high degree of sensitivity, as measured by skin tests. These circumstances may be in part responsible for the lesser effectiveness of these antigens. However, in our previous papers (1) (5) we have stressed the importance of the individual host factor in determining the occurrence of lesions of the periarteritis nodosa or rheumatic carditis type in the sensitized animals. Our subsequent experience has amply confirmed the great importance of this host factor, though the manner in which it operates is, at present, altogether as obscure as why some individuals who are sensitized to ragweed develop hay fever on exposure to the pollen, while others who are equally hypersensitive, as measured by skin tests, and who are equally exposed to the pollen, fail to develop hay fever. In view of this unpredictable host factor, we cannot be certain that egg albumin is a less effective antigen for the production of these lesions than is horse serum, for it is possible that a larger percentage of the rabbits treated with horse serum were inherently more susceptible to this type of reaction than were those treated with egg albumin. We hope that further studies, aided by selective inbreeding, may serve to clarify this point.

We believe that the lesions illustrated in Figs. 1 through 26, as well as those illustrated in our previous paper, correspond closely enough with the peculiar basic characteristics of the lesions of rheumatic carditis to render it highly probable that the latter may represent the results of focal hypersensitive reactions produced by a circulating soluble antigen. While not all of the manifold variations in the lesions of rheumatic carditis are reproduced precisely in the hearts of these

experimental animals, the essential process in the rabbits is so strikingly similiar in its basic qualities to that familiar in rheumatic carditis that it at least demonstrates that focal lesions of the rheumatic type (collagen damage with peripheral accumulation of cells of the Aschoff body type, valvular, endocardial, myocardial and pericardial inflammation and scarring) can result from hypersensitive reactions to a circulating antigen to which the body has become sensitized. In some instances the lesions are remarkably similar to or even identical with those of human rheumatic carditis. The experimental lesion shown in Figs. 10 and 11, for example, is virtually identical with the human lesion in Fig. 12; the circle of cells about a little focus of oedematous, damaged collagen in the rabbit of Fig. 7 is a familiar lesion of the Aschoff body type in human rheumatic hearts; the focal necrosis of several myocardial fibres with associated, bordering mononuclear cells in the lesions of Figs. 1, 2 and 3 are familiar characteristics of the myocardial Aschoff body in the human being, as shown in the basically identical human lesion in Fig. 4; the multinuclear cells in the experimental lesions of Figs. 9, 13 and 14 are altogether like the cells peculiar to the Aschoff body in human rheumatic lesions; and the thickening and scarring of the valve of the rabbit of Fig. 25, and of the chorda tendinea shown in Fig. 26, are replicas of lesions thoroughly familiar in rheumatic carditis.

It is well known that even in the human rheumatic heart the Aschoff bodies take many and varied forms. It is only the basic characteristics of focal collagen or myocardial damage with bordering mononuclear cells that is common to them, and these characteristics are found in the experimental lesions. If not all forms of the Aschoff body are precisely reproduced in the rabbit, it must be remembered that the lesions produced in animals by a specific etiological agent are often not identical with those produced in man by the same agent. Anyone familiar with human and experimental tuberculosis, for example, could differentiate at once between the tubercles produced by the tubercle bacillus in the rabbit and those familiar in human tuberculosis, though the basic characteristics of both are the same; and this applies also to the chancre produced by the treponema pallidum in the rabbit and in man. The essential point in a comparison of experimental and human lesions is not the absolute identity of form;

it is, rather, the identity of the type of reaction, *i.e.*, the character of the injury to the tissues and the character of the cellular and fluid response to the injury. We believe that, from this standpoint, the focal hypersensitive lesions produced in these animals by circulating antigens (horse serum; egg albumin) that possess virtually no primary toxicity, are sufficiently similar to those of rheumatic carditis to provide a strong support for the view that human rheumatic lesions may represent the results of focal hypersensitive reactions to one, or perhaps to a number of different soluble antigens, and to warrant the most careful further investigation of this possibility.

In a former paper (2), as was stated above, we pointed out and illustrated the basic identity of the peculiar lesion of rheumatic pneumonitis with that which occurs in human hypersensitive reactions to the sulfonamides, and we presented this as further evidence in support of the view that the rheumatic process represents a hypersensitive reaction. The essence of rheumatic pneumonitis is focal damage to the capillaries of the alveolar walls, and this results in one or in a combination of several of the following lesions: (1) thrombosis of the affected capillary; (2) focal exudation, often with the formation of a hyaline membrane that lines the alveolus; (3) focal haemorrhage; and, in severe lesions, (4) focal necrosis of the alveolar wall. In our experimental animals we have observed beautiful, focal alveolar capillary thrombosis precisely like that in human rheumatic pneumonitis, and also focal exudation. These lesions, and also a study of the joints, will be described and illustrated later. Their occurrence provides additional evidence for the hypersensitive nature of the entire rheumatic process.

During the course of the present studies we have observed the occurrence of many arterial lesions of the periarteritis nodosa type in animals subjected to the hypersensitive reactions. Evidence relating human periarteritis nodosa to hypersensitive reactions, and the experimental production of the condition by means of hypersensitive reactions of the serum sickness type have been described in our previous papers (3) (4) (5). Figs. 27, 28 and 29 illustrate further typical examples of the experimental lesions. Recently, Smith, Zeek and McGuire (6) have reported the occurrence of periarteritis nodosa in dogs and rats that were made hypertensive by wrapping the

kidneys with silk. They stressed the relation of infection of the operative site to the occurrence of the vascular lesions. Selye and Pentz (7) described periarteritis nodosa in rats that were unilaterally nephrectomized and given repeated injections of desoxy-corticosterone acetate. It was not stated whether or not the operative sites were infected. It should be mentioned that Willens and Sproul (8) found periarteritis nodosa in about 10 per cent of older rats, in which chronic infections are frequent. We have never encountered the spontaneous occurrence of this vascular lesion in any of the many hundreds of rabbits studied histologically in other experiments, nor did Smith and his coworkers (6) find in the literature any recorded instance of the spontaneous occurrence of the lesion in a rabbit. It may be stated that infections were not encountered in our rabbits that developed periarteritis nodosa after treatment with the foreign antigen, and that the kidneys and urine were normal in many of them.

SUMMARY

In preceding papers we have (a) described and illustrated cardiac lesions of the rheumatic type that were produced in animals by hypersensitive reactions to foreign protein; (b) shown the basic identity of rheumatic pneumonitis with the pneumonitis resulting from sulfonamide hypersensitivity in non-rheumatics; and (c) assembled evidence of a variety of other types in support of the view that human rheumatic lesions represent the results of focal hypersensitive reactions. In the present paper further experimental cardiac hypersensitive lesions of the rheumatic type are illustrated. Studies illustrating experimental hypersensitive pneumonitis and arthritis will be presented shortly.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Melanie W. Donaldson)

FIG. 1. Lesion of Aschoff body type in myocardium of rabbit R91PN6, sensitized to egg albumin. See Fig. 2.

FIG. 2. Higher magnification of Fig. 1.

FIG. 3. Lesion of Aschoff body type in myocardium of rabbit of Fig. 1. Compare with human lesion in Fig. 4.

FIG. 4. Aschoff body in myocardium of human case of acute rheumatic fever (Autopsy No. 18816). Compare with rabbit lesion in Fig. 3.

FIGS. 5 AND 6. Perivascular lesions of Aschoff body type in myocardium of rabbit R59PN3 and rabbit R10, both sensitized to horse serum.

FIGS. 7 AND 8. Early lesions of Aschoff body type (focal oedema and damage of collagen surrounded by mononuclear cells) in subendocardial connective tissue of rabbit R46PN2 and rabbit R48PN2, both sensitized to horse serum.

FIG. 9. Endocardial nodule of Aschoff body type, containing numerous multinuclear "Aschoff body cells" in rabbit R65PN3, sensitized to horse serum.

FIG. 10. Endocardial nodule (arrow) in rabbit R65PN3, sensitized to horse serum. See Fig. 11.

FIG. 11. Higher magnification of nodule in Fig. 10. Note the numerous cells with linear nuclear chromatin ("Anitschkow myocytes") familiar in human rheumatic lesions. Compare with human lesion in Fig. 12.

FIG. 12. Lesion from human case of acute rheumatic fever (Autopsy No. 15155), closely resembling lesion of rabbit in Fig. 11. Arrows point to "Anitschkow myocytes."

FIG. 13. Two multinuclear cells of Aschoff body type in endocardial lesion of serum-sensitized rabbit R65PN3. Cell at "A" has eight nuclei. Cell at "B" has two nuclei with the linear chromatin of the "Anitschkow myocyte."

FIG. 14. Multinuclear cells of Aschoff body type in endocardial lesion of serum-sensitized rabbit R65PN3. Cell at "A" has five nuclei; cell at "B" has three. Focus of degenerated collagen at "C".

FIG. 15. Focal lesions at base of valve leaflets of serum-sensitized rabbit R48PN2. See Figs. 16 and 17 for higher magnification.

FIG. 16. Higher magnification of lesion at base of valve leaflet on right side in Fig. 15. Note oedema and degeneration of collagen, bordered by mononuclear cells.

FIG. 17. Higher magnification of lesion at base of valve leaflet on left side in Fig. 15. Note oedema and degeneration of collagen bordered by palisade of mononuclear cells. Compare with human lesion in Fig. 18.

FIG. 18. Palisade of mononuclear cells bordering focus of oedematous, damaged collagen in endocardium of human case of acute rheumatic fever (Autopsy No. 18816). Note close resemblance to lesion in rabbit of Fig. 17.

FIG. 19. Focal oedema and degeneration of collagen, bordered by "Anitschkow myocytes" with linear arrangement of chromatin, in endocardium at base of valve in serum-sensitized rabbit R48PN2.

FIG. 20. Vegetation consisting of fibrinoid degeneration of collagen, oedema and mononuclear cells in valve of rabbit R283PN8, sensitized to equal parts of horse serum and egg albumin.

FIG. 21. Nodule in valve of serum-sensitized rabbit R48PN2.

FIG. 22. Nodule (arrow) in another valve of rabbit of Fig. 21. Note also diffuse inflammatory infiltrations in valve and mural endocardium.

FIG. 23. Palisade of mononuclear cells bordering focus of oedematous, damaged collagen in another valve leaflet of rabbit of Fig. 21.

FIG. 24. Focus of oedematous, damaged collagen bordered by mononuclear cells in valve of serum-sensitized rabbit R59PN3. Note swelling of endothelial cells.

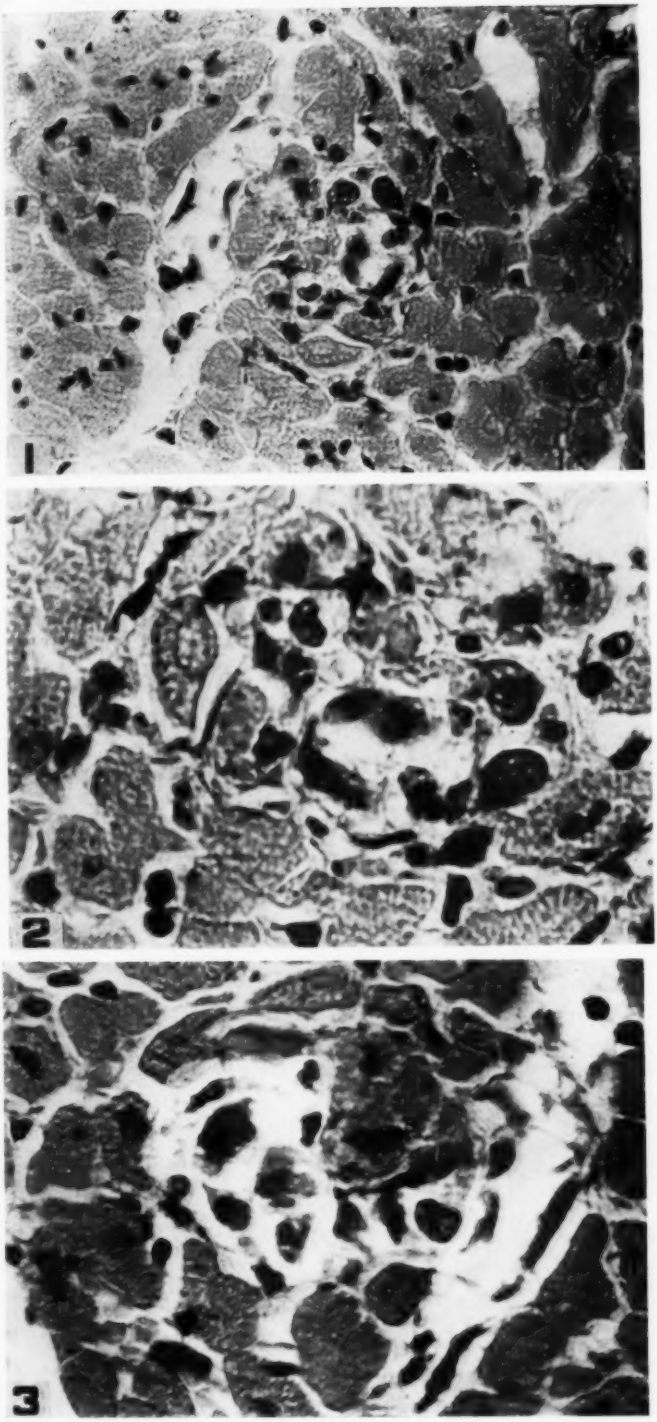
FIG. 25. Thickened, scarred and inflamed valve leaflet (A) in rabbit R59PN3. Compare with leaflet B, which is approximately normal in thickness. This rabbit received two injections of 10 cc. of horse serum per kg., and was killed 1 month after the first injection. The fresher lesion in Fig. 24 was probably the result of the second injection given 11 days before the rabbit was killed.

FIG. 26. Thickened, scarred and inflamed chorda tendinea (A) of rabbit of Fig. 25. The valve leaflet to which it is attached (B) is also inflamed and somewhat thickened.

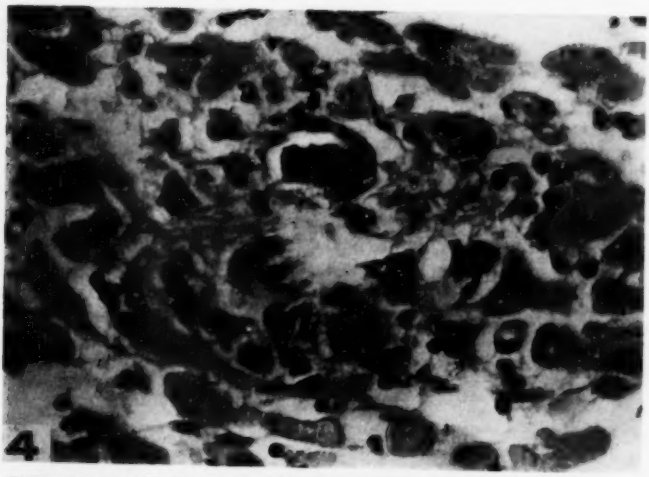
FIG. 27. Lesion of periarteritis nodosa in pericardial artery of serum-sensitized rabbit R52PN2.

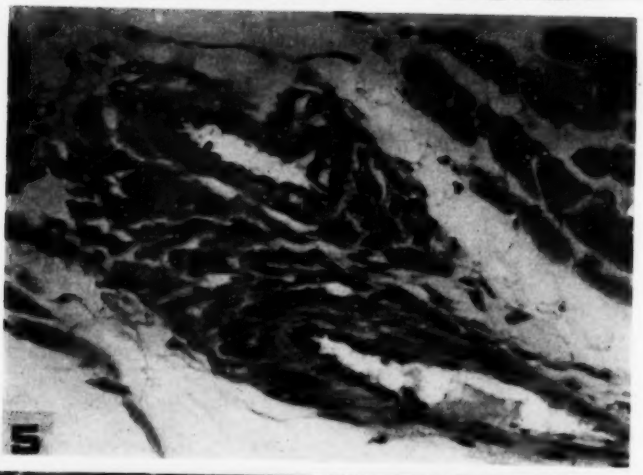
FIG. 28. Lesion of periarteritis nodosa in epicardial branch of coronary artery, with thrombotic obliteration of lumen, in serum-sensitized rabbit R64PN3.

FIG. 29. Periarteritis nodosa involving sharply a segment of the circumference of an epicardial branch of the coronary artery in serum-sensitized rabbit R52PN2.

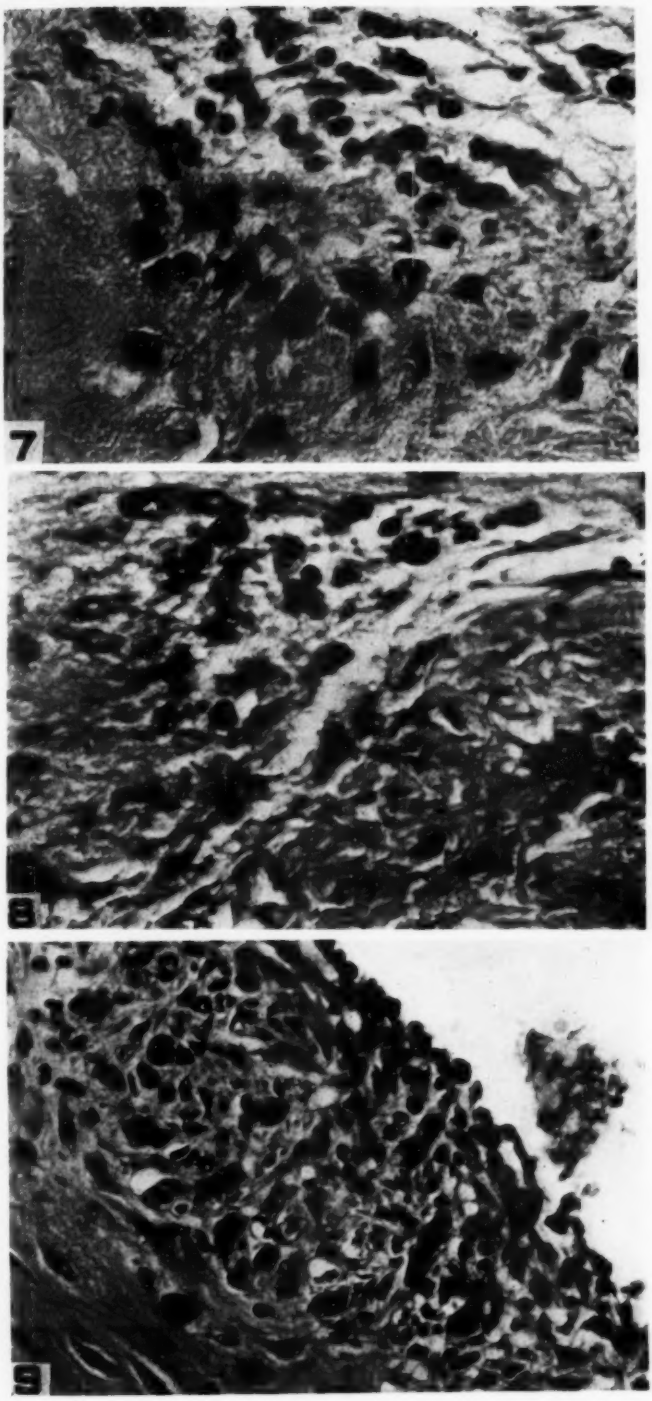


FIGS. 1–3

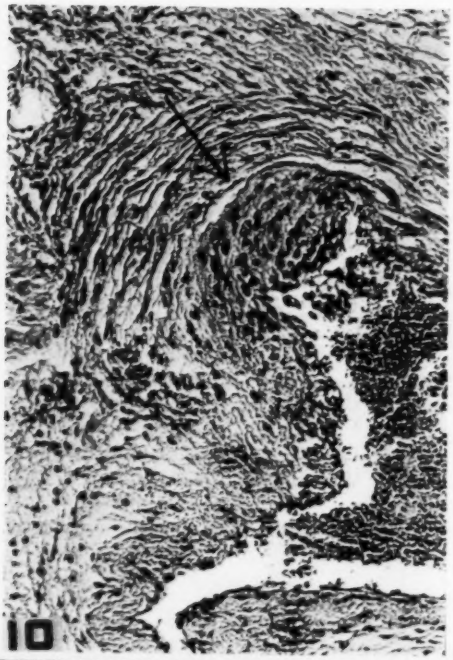


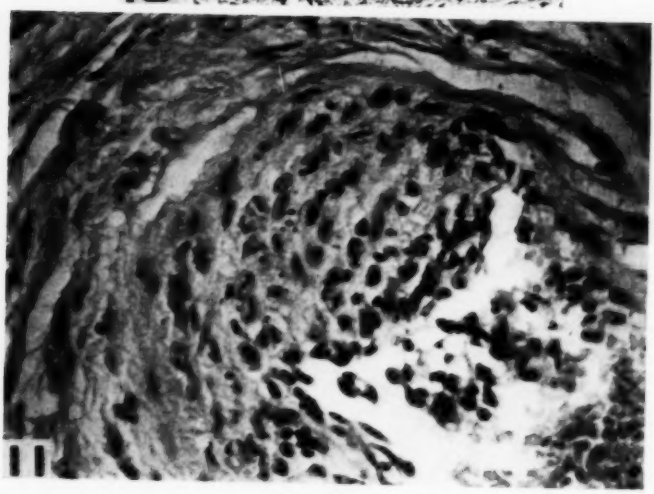


FIGS. 4–6

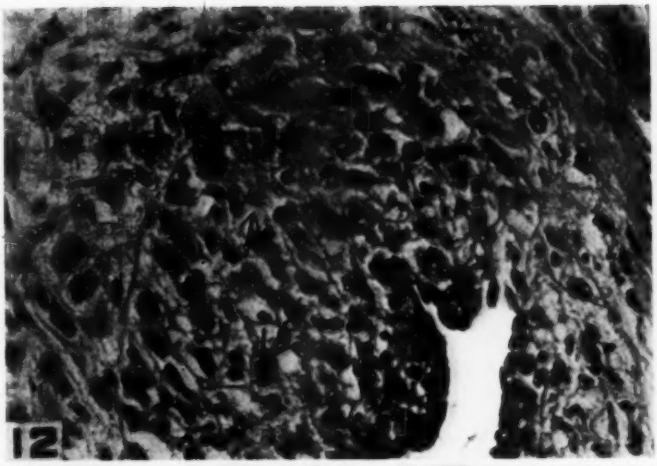


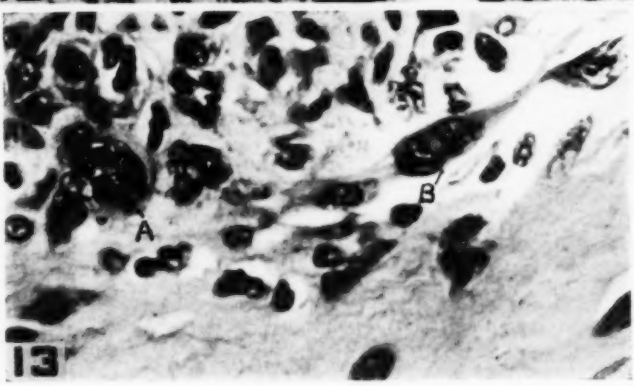
FIGS. 7–9



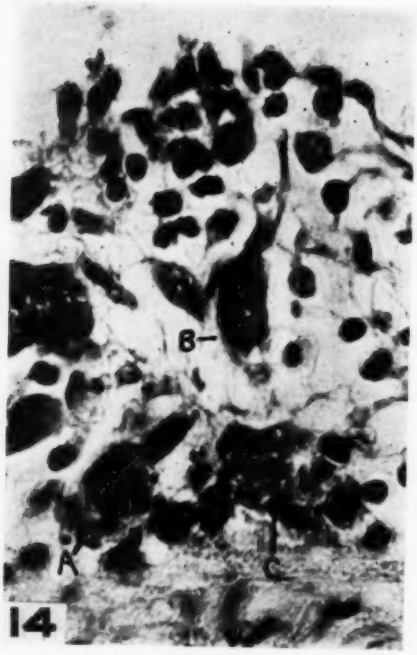


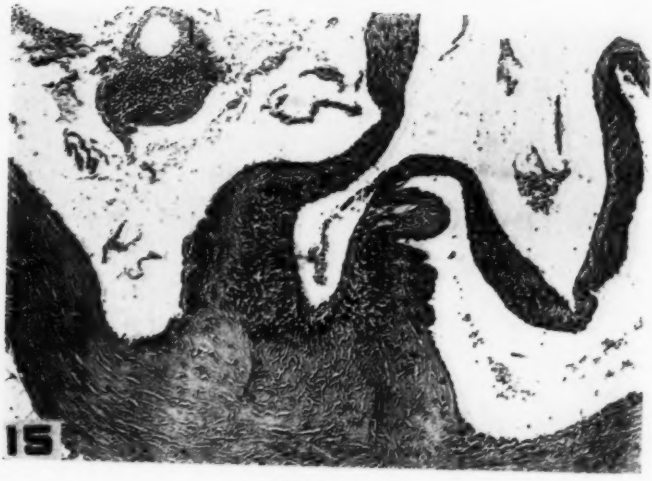
FIGS. 10–11



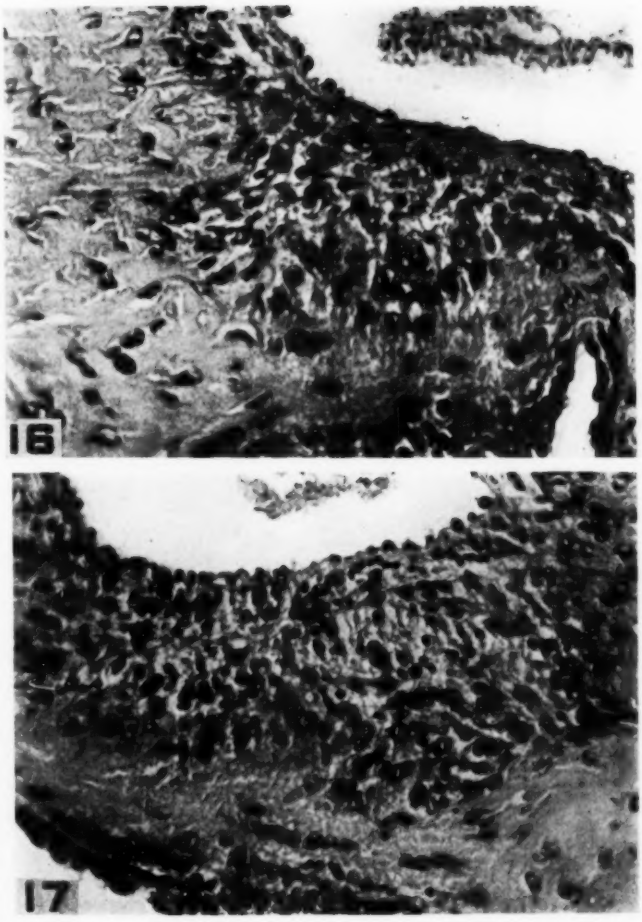


FIGS. 12–13





FIGS. 14–15



FIGS. 16–17

FIGS. 18–19

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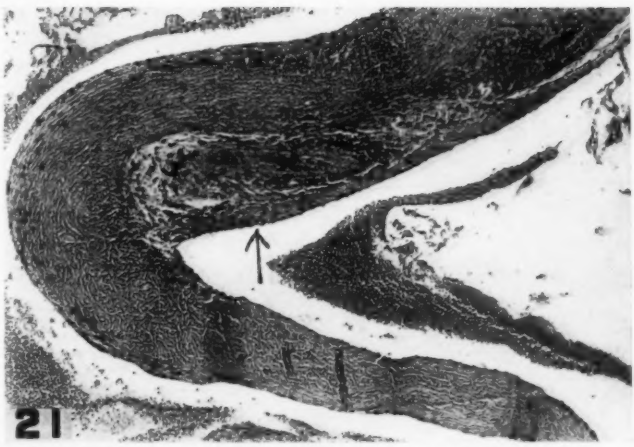

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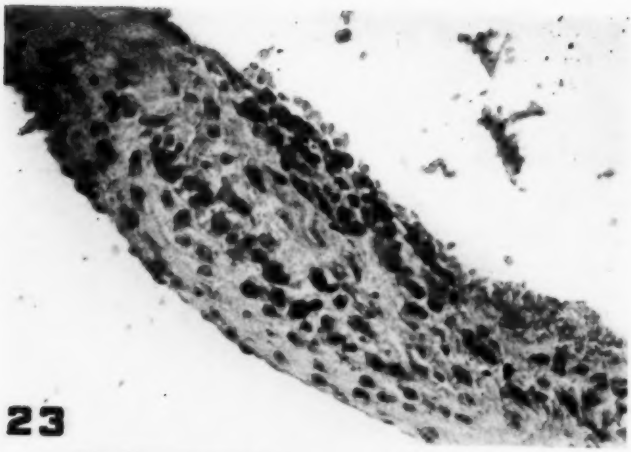
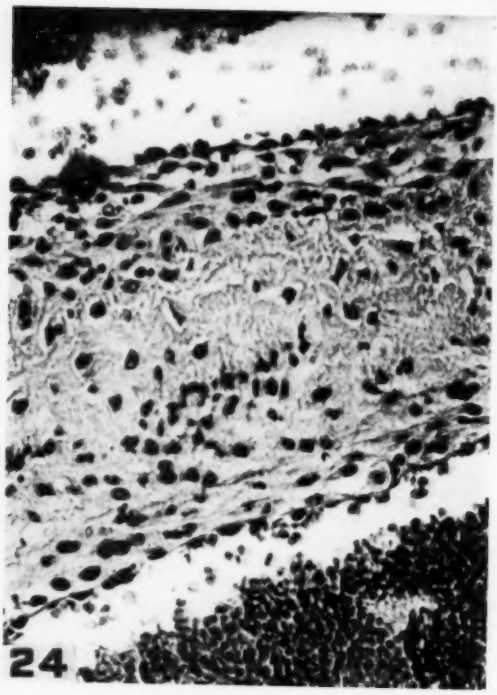
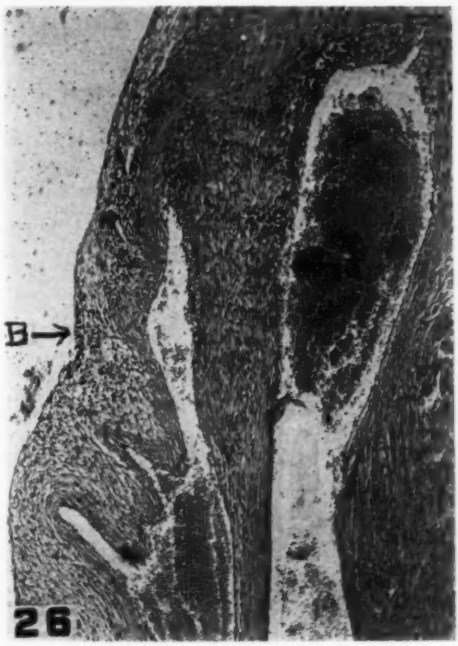
FIGS. 20–22

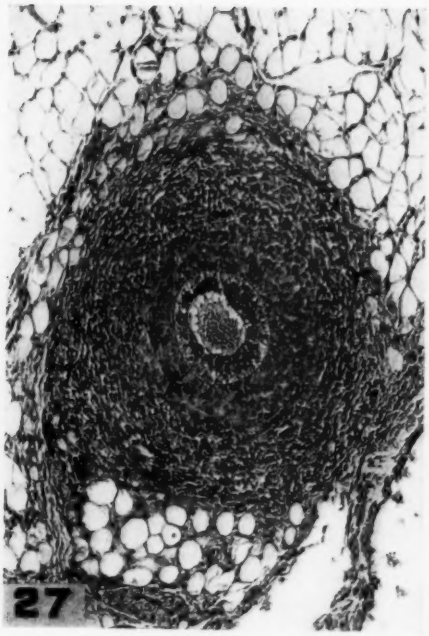


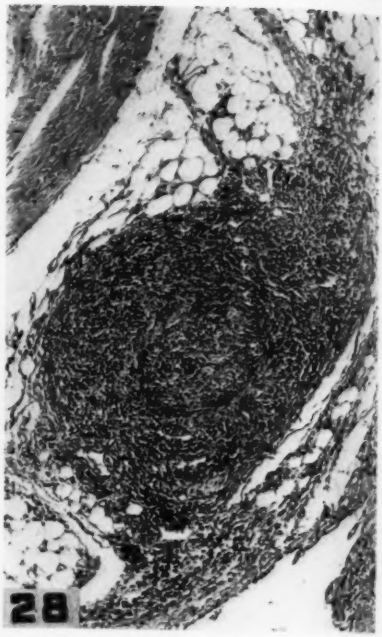


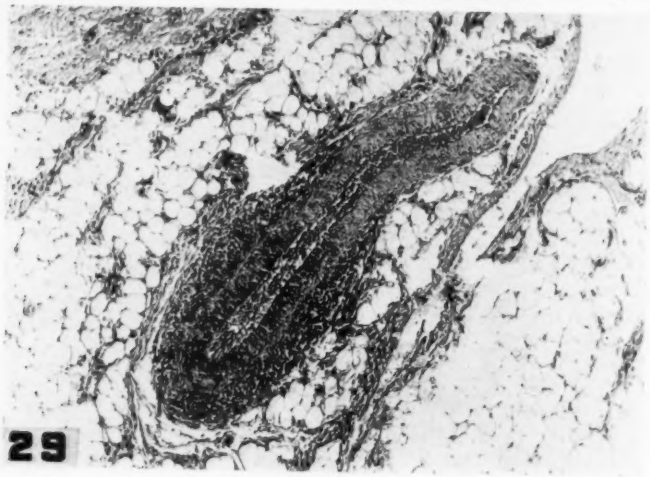
FIGS. 23–24



FIGS. 25–26







FIGS. 27–29

NON-PROTEIN NITROGEN AND PROTEIN CONCENTRATIONS OF SERUM AND CEREBROSPINAL FLUID IN SHOCK[1]

GEORGE W. DUNCAN, J. LOGAN IRVIN AND STANLEY J. SARNOFF

From the Departments of Surgery and Physiological Chemistry, The Johns Hopkins University, and The Johns Hopkins Hospital, Baltimore, Maryland

In recent years there have been numerous studies of the composition of body fluids of animals in a state of shock (1–4). The scope of this experimental approach has been limited somewhat because of difficulty in the collection of various fluids, other than blood, in amounts sufficient for satisfactory examination. However, the reports of Drinker (5) and Blalock (6) on the study of lymph from animals in shock are examples of the extension of these studies to the less easily accessible fluids.

Several investigations of problems related to shock have directed attention to possible alterations in the permeabilities of membranes, particularly capillary membranes, located at the site of the trauma (1) or in more general regions (2, 7). The importance of this subject provides incentive for the examination of other membranous barriers.

Although the barrier relationship between blood and cerebrospinal fluid differs considerably from that existing between blood and interstitial fluid (8), the cerebrospinal fluid is easily accessible and may reflect some of the general relationships and certain changes which occur in shock. The problem is approached in a preliminary manner in this paper by a comparison of the non-protein nitrogen and protein concentrations of serum and cerebrospinal fluid during experimental shock.

EXPERIMENTAL METHODS

The type of shock which appeared to be most suitable for this study was that produced by experimental crushing injury since it has been shown to be characterized by low blood pressure, progressive hemo-

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Johns Hopkins University.

concentration, evidence of renal damage, and death, unless treatment is instituted (9). Dogs weighing between 7 and 12 kilograms were used as experimental animals. Anesthesia was produced by subcutaneous injection of 0.03 grams of morphine per kilogram of body weight, followed thirty minutes later by 0.02 grams of nembutal per kilogram. The dose of morphine was repeated seven to nine hours later and 0.006 grams of nembutal per kilogram were given during the succeeding 18 to 24 hours. Mean arterial pressure was determined repeatedly by direct puncture of the femoral artery. The mechanical press was applied to a thigh of the animal for a period of 15 hours at a pressure of approximately 500 pounds. At the end of this time the press was removed, and the animal was observed until the arterial pressure had declined to a level of 50 to 60 mm. of mercury. In most instances, an attempt was made to maintain the animal in shock for the maximum period which still would allow time for collection of specimens of blood and cerebrospinal fluid before death occurred. A 10 ml. specimen of blood was withdrawn from the femoral artery for determination of total protein and non-protein nitrogen concentrations in the serum. Immediately thereafter the animal was turned to a prone position, and a midline incision was made in the upper cervical and lower occipital region exposing the interspinous ligament between the first and second cervical vertebrae. A 20-gauge needle was inserted through ligament and dura into the cistern and two 2-ml. samples of spinal fluid were withdrawn. Only slight suction was applied in withdrawing the fluid because of the ease with which hemorrhage into the spinal fluid could be induced. An incision was employed because small numbers of red cells were found occasionally in specimens obtained by direct puncture of the cistern.

In the initial phases of the study, an attempt was made to obtain specimens of spinal fluid at the beginning as well as at the end of the experiments. In spite of the desirability of this procedure, it was abandoned because the collection of an initial sample increased the possibility of hemorrhage into the spinal fluid. Considered also was the possibility of alteration of fluid equilibria by the withdrawal of the initial sample. Similar disturbances are well recognized by investigators of the aqueous humor of the eye in the so-called aqueous

of secondary formation which fills the anterior chamber following removal of a considerable fraction of the primary fluid (10). This difficulty in the collection of an initial as well as a final sample of spinal fluid prevented thorough study of the individual experimental animals and restricted the investigation to comparison of the analyses of samples from a group of animals in shock with those from a group of control animals. Data for the two groups were analysed by the statistical procedure described by Snedecor (11). Cell counts were performed on all specimens of spinal fluid, and those specimens which contained more than an occasional erythrocyte or more than the normal number of leukocytes were discarded.

The animals of the control group were given the same amount of anesthetic and were restrained on the table for a period of time equal to the experimental periods for the animals in which shock was produced. The specimens of blood and cerebrospinal fluid were collected from these animals by the same procedure. Initial as well as final samples of blood were collected from some of the animals in each group.

The concentration of total protein in serum was calculated from the protein nitrogen determined by the general procedure of Howe (12), adapted for micro technique. Protein nitrogen was estimated by difference between the total nitrogen and the non-protein nitrogen of the serum. Total nitrogen was determined by a micro Kjeldahl procedure involving the absorption of ammonia in boric acid followed by titration with 0.01 N hydrochloric acid according to the method of Meeker and Wagner (13) with adaptations from Conway and Boyne (14). Non-protein nitrogen was determined by the method of Folin and Wu (15), with the modified reagent of Koch and McMeekin (16). Analyses were conducted in duplicate or triplicate.

The concentrations of non-protein nitrogen and protein in samples of spinal fluid were determined by an adaptation[2] of the procedure suggested in outline form by Peters and Van Slyke (17). The accuracy of the modified method was examined before application to the study of shock. In table 1 there are presented the results of the use of this modified method in the determination of protein in pooled

[2] This modified method will be described in greater detail in a subsequent publication.

samples of spinal fluid of man. The probable error of a single determination is ±4.3 per cent for samples in the normal range of protein concentrations. The accuracy of the method was determined further by analyses of samples of serum of known protein concentrations, which had been diluted with 0.85 per cent sodium chloride solution in order to simulate the concentration of protein in spinal fluid. Analytical recoveries were satisfactory (table 2).

TABLE 1

Determination of protein in pooled samples of spinal fluid of man

DESIGNATION OF POOLED SAMPLE OF SPINAL FLUID	NUMBER OF ANALYSES	MEAN CONCENTRATION OF PROTEIN IN SPINAL FLUID	PROBABLE ERROR OF THE MEAN	PROBABLE ERROR OF A SINGLE DETERMINATION
		mgms. per 100 mls.	*mgms. per 100 mls.*	*per cent*
1	9	32.3	±0.51	±4.7
2	10	29.0	±0.40	±4.3
3	10	22.1	±0.29	±4.1
4	4	17.6	±0.33	±3.8
5	4	25.4	±0.61	±4.8

TABLE 2

Determination of protein in samples of serum diluted with 0.85 per cent sodium chloride solution to simulate the protein concentrations of spinal fluid. The calculated concentrations are based on the determination of protein in the original sample of serum.

CALCULATED CONCENTRATION OF PROTEIN IN SAMPLE	NUMBER OF ANALYSES	MEAN CONCENTRATION OF PROTEIN (FOUND)
mgms. per 100 mls.		*mgms. per 100 mls.*
22.1 ±0.2	4	21.8 ±0.4
31.0 ±0.3	10	30.7 ±0.4
51.7 ±0.5	4	52.2 ±1.1
77.5 ±0.8	4	76.6 ±1.4
155.0 ±1.6	4	154.9 ±2.6

Comparative analyses have demonstrated that this method is more accurate than the nephelometric method of Looney and Walsh (18) or the procedure of Johnson and Gibson (19).

DISCUSSION

In tables 3 and 4 data obtained from twenty-five experiments are recorded. In the control experiments in which the animals were anesthetized and restrained by the method and for the length of time employed in the traumatized group, no evidence of shock was ob-

served. Arterial pressures were not altered significantly in any animals of this group, and hematocrit determinations did not deviate appreciably from initial values. Comparison of final with initial values for the concentrations of non-protein nitrogen and protein in serum indicated that the small changes which occurred were not significantly greater than those which are observed in analyses of samples collected at different times from the same normal, unanesthetized animal. The collection of cerebrospinal fluid specimens

TABLE 3

Control experiments in which animals were anesthetized and restrained

EXPT. NO.	MEAN ARTERIAL PRESSURE (MM. OF Hg)		HEMATOCRIT (VOLUME OF RED CELLS) PER CENT		TOTAL PROTEIN CONCN. OF SERUM (GMS. PER 100 ML.)		N.P.N. CONCN. OF SERUM (MGMS. PER 100 ML.)		PROTEIN CONCN. OF CEREBROSPINAL FLUID (GMS. PER 100 ML.)	N.P.N. CONCN. OF CEREBROSPINAL FLUID (MGMS. PER 100 ML.)
	Initial	Final	Intitial	Final	Initial	Final	Initial	Final	Final	Final
1	120	116	46	47	5.6	6.9	27.9	27.5	0.031	13.7
2	110	116	46	43	6.2	6.1	40.5	30.8	0.028	14.1
3	128	120	39	36	7.1	7.3	23.6	24.8	0.032	14.4
4	122	112	40	39	8.0	7.6	22.2	31.8	0.030	16.2
5	130	116	48	50	6.2	6.4	25.6	28.7	0.020	16.1
6	120	116	40	43		5.7		38.7	0.027	24.5
7	126	120	56	54		5.6		27.3	0.030	17.0
8	108	112	54	50		6.0		37.6	0.027	22.4
9	112	106	43	42		6.8		29.1	0.036	22.2
10	118	122	57	55		7.1		18.7	0.018	19.9
11	110	112	36	40		6.5		24.3	0.019	21.6
Mean						6.6		29.0	0.027	18.4
$S_{\bar{x}}$						±0.6		±1.7	±0.002	±1.2

$S_{\bar{x}}$ is the standard deviation of the mean.

from these animals was much easier than collection from those which had not been subjected to crushing injury, and at autopsy no gross diminution in the amount of fluid was observed. The mean concentrations of non-protein nitrogen and protein in spinal fluid of the control animals are in general agreement with those which have been recorded for normal animals (8).

All of the fourteen animals subjected to crushing injury demonstrated progressive evidence of shock following the removal of the

press at the end of a period of fifteen hours. There was progressive swelling of the injured thigh, progressive fall in arterial pressure, progressive hemoconcentration and evidence of renal damage. The time of collection of specimens of cerebrospinal fluid and blood, accomplished after development of severe shock, varied from three to eight hours after removal of the press. The collection of cerebrospinal fluid specimens from animals in shock was more difficult than the

TABLE 4

Examination of animals in shock produced by crushing injury

EXPT. NO.	MEAN ARTERIAL PRESSURE (MM. OF Hg)		HEMATOCRIT (VOLUME OF RED CELLS) PER CENT		TOTAL PROTEIN CONCN. OF SERUM (GMS. PER 100 MLS.)		N.P.N. CONCN. OF SERUM (MGMS. PER 100 MLS.)		PROTEIN CONCN. OF CEREBRO-SPINAL FLUID (GMS. PER 100 ML.)	N.P.N. CONCN. OF CEREBRO-SPINAL FLUID (MGMS. PER 100 MLS.)
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Final	Final
1	120	20	39	66	6.7	8.2	26.4	59.5	0.048	26.4
2	110	45	38	62	7.3	9.2	34.1	60.0	0.020	24.2
3	115	50	43	56	6.9	9.0	31.3	44.5	0.041	18.1
4	126	55	47	62	6.6	7.2	40.5	53.2	0.037	31.3
5	130	30	44	53	6.0	7 1	27.4	69.6	0.038	36.0
6	112	60	41	50	6.4	7.3	26.0	59.0	0.035	34.2
7	105	55	43	51	6.4	7.6	28.0	80.0	0.030	45.0
8	115	40	40	47	5.9	8.6	22.2	85.0	0.040	42.0
9	110	65	42	56		5.6		58.4	0.028	33.7
10	112	55	44	58		6.5		77.8	0.042	41.1
11	135	30	42	54		8.7		118.3	0.032	54.4
12	120	65	50	55		7.9		59.8	0.049	24.4
13	128	60	39	44		6.3		48.1	0.027	23.8
14	122	45	48	64		8.8		78.0	0.027	35.0
Mean						7.7		68.0	0.035	33.6
Sx						±0.3		±5.1	±0.002	±2.6

collection from the control group, and at autopsy the ventricles and the spinal subarachnoid space showed gross diminution of fluid in a majority of the cases. The pathological features of other organs were similar to those previously described (9). In those cases in which serum protein concentrations and hematocrit levels were determined at the beginning of the experimental periods, comparison with final concentrations demonstrated a significant increase in every

instance (table 4). Also there was a significant increase in the concentration of non-protein nitrogen in the sera of these cases.

The mean values for the terminal concentrations of both non-protein nitrogen and protein in the sera of the animals in shock were significantly greater statistically than those of the control group. Similarly, the mean concentration of non-protein nitrogen of spinal fluid was significantly greater for the traumatized animals. Thus it appears that an increase in the concentration of non-protein nitrogen in serum during shock is accompanied by a concomitant rise in the N.P.N. concentration of cerebrospinal fluid. This is not unexpected in view of the reports of Galan and Houssay (20) and Cockrill (21) that an experimentally induced increase in the concentration of urea in blood is followed by a slow, parallel rise in the urea concentration of cerebrospinal fluid.

In a review of the subject of cerebrospinal fluid Flexner (8) has assembled data which appear to prove conclusively that in normal animals the concentrations of urea, creatinine, uric acid, and amino acids in plasma are definitely greater than the respective concentrations of these constituents in cerebrospinal fluid. Inasmuch as these nitrogenous compounds are the principal constituents of the non-protein nitrogen fraction of both serum and cerebrospinal fluid, it is reasonable to suppose that in normal animals the ratio of the mean concentration of non-protein nitrogen of serum to that of spinal fluid is greater than one. This supposition is supported by the limited amount of available data (22). For our group of control animals the mean ratio of the concentration of non-protein nitrogen of serum to that of cerebrospinal fluid is 1.58, and the corresponding ratio for the group of animals in shock is 2.02. When calculated on the basis of the average water content of serum and cerebrospinal fluid, the ratios are 1.76 and 2.26, respectively. These data are in agreement with Flexner's general conclusion (8) that cerebrospinal fluid is not a dialysate in equilibrium with blood plasma, although it is recognized that data for the distribution of a mixed fraction are of less value in this connection than information concerning the distribution of single substances. From the standpoint of the objective of the present investigation, the distribution ratios for non-protein nitrogen for the two groups suggest that gross alteration of

the barrier relationship between blood plasma and cerebrospinal fluid did not occur under the conditions of these experiments. The small, but significant, increase in the distribution ratio during shock may be explained reasonably as due to a lag in the normal transfer and distribution of non-protein nitrogenous substances across the barrier. In this connection, attention is directed again to the previously mentioned experiments of Galan and Houssay (20) and of Cockrill (21).

The mean concentration of protein in the cerebrospinal fluid of the animals in shock was greater than the corresponding value for the control group. However, this increase was of small magnitude and may be explained on the basis of a slight shift of water from the spinal fluid resulting from the hemoconcentration. The mean ratios of the concentrations of protein in serum to the corresponding concentrations in cerebrospinal fluid were essentially the same for both groups of animals. These experiments indicate that if alteration in the barrier relationship between plasma and cerebrospinal fluid does occur in shock produced by this method, it is not sufficient to permit extensive passage of plasma proteins into the spinal fluid.

SUMMARY

Experiments are described in which the concentrations of non-protein nitrogen and protein in serum and cerebrospinal fluid of animals in shock produced by crushing injury are compared with those of a control group. The mean concentrations of both non-protein nitrogen and protein in serum and cerebrospinal fluid were found to be significantly greater in the animals in which shock was produced. The mean ratios of the concentrations of non-protein nitrogen in serum to the corresponding values in spinal fluid were 1.58 for the control group and 2.02 for the group of animals in shock. The mean ratios of the concentrations of protein in serum to the corresponding concentrations in cerebrospinal fluid were essentially the same for the two groups.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

The Hemorrhagic Diseases and the Physiology of Hemostasis. By ARMAND J. QUICK. 340 pp., Illus. $5.00. Charles C. Thomas, Springfield, 1942.

The purpose of this monograph "is to present and to correlate the experimental and theoretical aspects of hemostasis and to summarize the present knowledge concerning the important hemorrhagic diseases." The first half is devoted to the agents participating in the regulation of bleeding, namely: thrombin, prothrombin, fibrinogen, thromboplastin, platelets and anticoagulants. The fundamental researches dealing with these substances are described. The latter half of the monograph is devoted to a discussion of the principal hemorrhagic diatheses, namely: thrombocytopenic purpura, hereditary hemorrhagic diatheses, afibrinogenemia, hemophilia, hemorrhagic diathesis of avitaminosis K and toxic sweet clover disease. In the appendix a group of methods are described which are "primarily intended for practical clinical studies."

The monograph is well organized, authoritative and clearly written and is easily readable. The present knowledge of the fundamental factors of the coagulation of the blood and of the physiology of hemostasis is well summarized. The approach is more physiological than clinical and the descriptions and diagnoses of the principal hemorrhagic diseases are not as adequately treated as the physiology. However, the excellent presentation of fundamental physiology and chemistry should make this a valuable adjuvant to the standard textbooks on hematology. This book can be recommended to students of physiology and medicine.

G. E. C.

Vascular Responses in the Extremities of Man in Health and Disease. By DAVID I. ABRAMSON. 382 pp. $5.00. The University of Chicago Press, Chicago, 1944.

This volume was apparently written around the extensive experience of the author with the venous occlusion plethysmograph. For that reason the physiological rather than the clinical approach has been taken in describing the responses of blood vessels in different portions of the extremities and their reaction to various pharmacological agents such as hormones, gases, vasodilator and vasoconstrictor substances. Because of this physiological approach, the book is particularly valuable to clinicians. A good feature of the book is a list of well chosen references at the end of each chapter. The difficult subject of edema unfortunately did not receive a great deal of attention. The book is a welcome addition to the library of any one interested in peripheral vascular diseases.

F. C. L.

Heart Disease. By PAUL DUDLEY WHITE. 976 pp. $9.00. 3rd Edition. The Macmillan Company, New York, 1944.

In bringing this classical text up to date the author has spared no pains and has even gone so far as to add in an appendix a series of notes on important work that appeared while the book was in the process of publication. New material included in the present edition includes an excellent chapter on "the range of the normal heart" and new sections on many other topics including pulmonary embolism, intracardiac thrombosis, phonocardiography, splanchnic resection for hypertension and cardiac problems of military service. There is no doubt that the new edition will be greeted with the general approbation accorded to its predecessors.

L. E. H.

Civilization and Disease. By HENRY E. SIGERIST. 255 pp. Illus. $3.75. Cornell University Press, Ithaca, N. Y., 1944.

An interesting and timely book, "Civilization and Disease" portrays the impact of disease on civilization in its various aspects as well as its different stages of development. The first chapter is devoted to the influence of civilization on disease. As man developed from a cave dweller to a highly social complex being, he was subjected to new health hazards. Migration, famines, congestion in cities, and restricted dietary habits all helped promote the spread of disease. On the other hand, improved methods of water supply, sewage disposal, housing and, above all, medical science and public health reduced considerably the incidence of many diseases.

In the next ten chapters the interrelationship between disease and the different aspects of human society are discussed with a sincere approach. Dr. Sigerist begins with the all important economic aspect. It is easy to see how disease can affect the economic status of the individual because a patient is certainly not a productive member of society. But the author analyzes in a logical and convincing manner the economic factors that breed disease. This culminates in the inescapable fact that the incidence of illness is largely determined by the economic status of the individual. That being the case, the reader is led to the logical conclusion that elevation of the standard of living is just as vital as any public health measure we have at our disposal, if not more so.

The interrelationships between disease and social life, law, history, religion, philosophy, science, literature, art and music are thoroughly and systematically explored at length. One chapter is devoted to each topic.

Finally in the concluding chapter, "Civilization Against Disease," the author brings forth the sobering warning, "We need a system of health services that reaches everybody. Greater organizational problems have been and are being solved, particularly in these very days of war. We have all the money we need when we are attacked by a ruthless enemy. Disease is also an enemy. The health and welfare of every individual is the concern of society."

V. A. N.

Traumatic Injuries of the Facial Bones. By JOHN B. ERICH and LOUIE T. AUSTIN. 600 pp. $6.00. Saunders, Philadelphia, 1944.

Only during recent years has the treatment of fractures of the facial bones received the attention it deserves. Too often it has been extemporized on the basis of the training and inclination of the surgeon in charge whose background might be that of the general surgeon, the laryngologist, the plastic surgeon, the oral surgeon, or the brain surgeon. Specialized training in maxillo-facial surgery, which includes all of these backgrounds, has been exceptional. This book is an extremely successful attempt to produce a manual which will be a guide for those whose training in this regard is insufficient.

As Balfour says in his foreword, "The principles of plastic surgery are best exemplified in the management of maxillo-facial injuries and deformities, where the accomplishment of satisfactory results demands intelligent planning, perfect technic and exacting attention to every detail." Erick and Austin have produced in a relatively small book their plans of treatment and have supported their suggestions by what seems to be a complete coverage of all relevant details. Their collaboration as plastic surgeon, otolaryngologist and dental surgeon is unusually realized. Perhaps the most remarkable features are the illustrations of the moulages of Bulbulian which were utilized in the instruction of those officers of the armed forces who have been assigned to the Mayo Foundation for training in maxillo-facial surgery. It is scarcely necessary to add that this book is highly recommended.

E. M. H.

Proceedings of the Conference on Problems of Human Fertility. Edited by EARL T. ENGLE. 182 pp. $1.50. Published by the National Committee on Maternal Health, New York, 1943.

This small volume covers the proceedings of the 1943 conference on human fertility sponsored by the National Committee on Maternal Health. It consists of papers presenting new work in human reproduction supplemented by discussion of the topics by leading workers in the field.

The first section deals with criteria of ovulation and presents the endocrine criteria, evidence derived from study of ova and early embryos, correlation of corpus luteum age and ovulation and the current status of electrometric data. Another section considers sperm migration and survival and the biology of the vagina. The final section is devoted to the placenta, including the cytology of the trophoblast and studies on placental transmission of hormones, metabolites, chemotherapeutic agents, radioactive isotopes and native proteins with their associated problems of sensitization and immunization.

Research workers in reproductive physiology will find this book stimulating both for the facts presented and for the challenging conjectures and suggestions offered in discussion. It will be of interest also to clinicians who wish to keep abreast of current concepts.

E. D.

Virus Diseases in Man, Animal and Plant. By GUSTAV SEIFFERT. 323 pp. $5.00. Philosophical Library, Inc., New York, 1944.

As stated in the author's preface, this book is a survey of the most important literature concerning viruses and virus diseases. Unfortunately it covers the period from 1892 through 1937 only. This fact considerably reduces the value of the book, for while most of the fundamental work was done during this period, many contributions of considerable worth have been made in the past six years.

The content of the volume and the statements of the author emphasize the necessity for consideration of all the virus diseases of man, animals, insects and plants in the formation of a clear concept of the nature of these diseases and the problems that surround them.

This emphasis on the need for a comprehensive point of view constitutes the chief value of the book. There is also, of course, an extensive bibliography.

The translation is not good. The sentence structure and choice of words are often confusing.

J. E. G.

Intracranial Arterial Aneurysms. By WALTER E. DANDY. Pp. 147. $2.50. Comstock Publishing Co., Ithaca, New York.

This is an excellent book with a wealth of valuable information. It reveals Dr. Dandy's extraordinary surgical skill and his great capacity for original investigation. Some years ago he became interested in intracranial aneurysms and within a short time learned how to recognize them. He soon devised a surgical technique by which they could be exposed and cured by ligation of the affected arteries. These statements apply, of course, more especially to aneurysms of the internal carotid artery. Since then he has accumulated a large number of cases among which are some of unusual interest.

This book presents his experience with the operative treatment of intracranial aneurysms and also a very complete analysis of similar cases collected from medical literature. It will be a long time before anything of importance can be added to the subject.

F. R. F.